

# **An analysis of antidepressant non-compliance in the private health sector of South Africa**

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## **PREFACE**

The current research thesis was written up in article format as required the regulations of the North-West University. Therefore, the findings of the study will be presented in Chapter 3 as research articles. The first three articles were accepted for publication, while the last of the four articles is still under review. All four articles were submitted for peer review in the following journals:

- Human Psychopharmacology: Clinical and Experimental
- South African Medical Journal
- AIDS Research and Therapy
- BioMed Central Psychiatry

For the sake of completeness, each article will contain a list of references used in the article according to the referencing style required by the particular journal in which it was published. The last chapter will contain a comprehensive bibliography listing all the references used in this thesis.

The layout of this thesis is as follows: Chapter 1 will consist of the research proposal as well as a comprehensive discussion of the methodology used. Chapter 2 will deal in depth with the literature regarding the development, treatment and co-morbid illnesses associated with major depressive disorder. As mentioned above, Chapter 3 will consist of four research articles portraying the results of the current research, and lastly, Chapter 4 will summarise the recommendations, conclusions and limitations of this research study.

The promoter and co-promoters who were also co-authors of the written articles have given their consent that these research papers can be part of this thesis. On the next the page, the authors' contributions will be described in detail.

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## ABSTRACT AND KEYWORDS

### **An analysis of antidepressant non-compliance in the private health sector of South Africa.**

The main aim of the thesis was to measure antidepressant (AD) non-compliance, to determine which factors are closely associated with AD non-compliance and the consequences of prolonged AD non-compliance in the private health sector of South Africa. The empirical study followed an observational, prospective, cohort study using longitudinal medicine claims data provided by a nationally representative Pharmaceutical Benefit Management company (PBM) from 1 January 2006 to 31 December 2011.

Failure to respond to AD treatment and achieving remission has severe neurobiological and clinical consequences. The clinical consequences include increased social and functional impairment, higher risk for recurrence and relapse of a depressive episode, a weak treatment outcome, significant increase in treatment cost, over-utilization of health care systems, and ultimately an increased suicide risk. However, the neurobiological consequences are much more far reaching. One of the more serious yet under-recognized neurobiological complications of AD non-compliance is the development of antidepressant discontinuation syndrome (ADS), which is the result of non-compliance or the abrupt discontinuation of AD treatment. Altered serotonergic dysfunction appears central to ADS so that how an antidepressant targets serotonin will determine its relative risk for inducing ADS and thereby affect later treatment outcome. Low ADS risk with agomelatine versus other antidepressants can be ascribed to its unique pharmacokinetic characteristics as well as its distinctive actions on serotonin, including melatonergic, monoaminergic and glutamatergic-nitrergic systems.

After the first four months only 34% (n=12 397) of patients were compliant. What's more a statistically significant association was found between active ingredient consumed and compliance ( $p < 0.0001$ ). Only 26.2% of patients who received amitriptyline-containing products were compliant compared to 38.8% and 38.7% in the cases of venlafaxine and duloxetine, respectively. The current study found that females have a significantly higher prevalence of MDD and HIV/AIDS when compared to males.

The co-morbidity between HIV/AIDS and major depressive disorder (MDD) had a significant effect on AD treatment compliance as patients diagnosed with both HIV/AIDS and MDD (74.43.  $\pm$  32.03, 95%CI: 71.51-77.34) displayed a lower compliance vs. MDD patients (80.94%  $\pm$  29.44, 95%CI: 80.56-81.33). Noteworthy, observations were that 75% ( $p < 0.0217$ ; Cramer's  $V = 0.0388$ ) of venlafaxine and 28.6% ( $p < 0.0197$ ; Cramer's  $V = -0.0705$ ) of the paroxetine items were compliant in patients diagnosed with both HIV/AIDS and MDD.

The overall compliance (35.19% acceptable compliance; n = 42 869) of patients taking both ADs and GDs was weak. In the group receiving both AD and GDs, an increased AD treatment period was associated with a significant increase ( $p < 0.0001$ ) in AD compliance (406.60 days; 95%CI: 403.20 – 409.90 vs. 252.70 days; 95%CI: 250.20 – 255.20). In this cohort amitriptyline (29.57%), mirtazapine (31.36%) and fluoxetine (32.29%) were associated with the lowest levels of compliance, while duloxetine (40.67%) was found to have the highest compliance. Lastly, ADs with highest non-compliance were associated with an increase use in GDs. Alprazolam (n = 10 201) and zolpidem (n = 9 312) were the most frequently dispensed GDs in combination with AD treatment.

In conclusion the current study confirms that AD non-compliance is as big an obstacle in developing countries as it is in developed countries. Antidepressant treatment non-compliance has far reaching

consequences especially with the development of ADS which further complicates MDD and might be a precursor for the development of TRD. Several factors were found to be closely associated with AD treatment non-compliance which include; pharmacological class of AD, gender, chronic co-morbid illnesses and a short treatment period.

**KEYWORDS:** Antidepressants, compliance, medicine possession ratio, major depressive disorder, South Africa, half-life; anhedonia; anxiety; serotonin transporter; phasic receptor occupancy; neuroplasticity, HIV/AIDS, Venlafaxine, GABAergic drugs and treatment-resistant depression.

## UITTREKSEL EN TREFWOORDE

### ’n Analise van antidepressant nie-meewerkendheid in die privaatgesondheidssektor van Suid-Afrika.

Die sleuteldoelwitte van die proefskrif is om antidepressant (AD) nie-meewerkendheid te bepaal, watter faktore dra by tot nie-meewerkendheid en die nagevolge van langdurige AD nie-meewerkendheid in die privaat gesondheidssektor van Suid-Afrika. ’n Beskrywende, prospektiewe kohort studieontwerp is gebruik vir die empiriese deel van die studie. Die data vir die studie is verkry vanaf ’n nasionaal verteenwoordigende Farmaseutiese Voordelebestuursmaatskappy, vir die tydperk 1 Januarie 2006 tot 31 Desember 2011.

Met die mislukking van AD behandeling of as ’n pasiënt nie in remissie gaan nie het ernstige kliniese en neurologiese nagevolge. Die kliniese nagevolge sluit die volgende in; verlaagde sosiale en funksionering, verhoogde risiko vir herhaling of terugval van ’n depressiewe episode, swak siekte prognose, oorgebruik van die gesondheidsstelsel en selfmoord op die uiteinde. Verder, die neurologiese nagevolge is baie meer skadelik as wat mens sal verwag. Een van die mees onderskatte gevolge van nie-meewerkendheid is die ontwikkeling van antidepressant onttrekkingsindroom. Veranderde serotonergiese funksionering speel waarskynlik ’n sentrale rol in die ontwikkeling van antidepressant onttrekkingsindroom. Die meganisme waarvolgens ’n geneesmiddel serotonien teiken bepaal die relatiewe risiko van ’n AD om antidepressant onttrekkingsindroom te veroorsaak en so doende ook die behandelingsuitkoms te affekteer. Die verlaagde risiko van agomelatien om antidepressant onttrekkingsindroom te veroorsaak kan toegeskryf word aan die geneesmiddel se unieke farmakokinetiese eienskappe asook agomelatien se kenmerkende aktiwiteit op serotonien. Verder werk agomelatien ook in op die melatonergiese, monoamienergiese en die glutamaatargies-stikstofsisteme.

Na die eerste vier maande is gevind dat slegs 34 % ( $n = 12\ 397$ ) van alle pasiënte meewerkend was ten opsigte van hulle AD behandeling. ’n Statisties betekenisvolle ( $p < 0.0001$ ) assosiasie tussen die aktiewe bestanddeel en meewerkendheid is gevind. Slegs 26.2% van alle pasiënte wat amitriptilien geneem het, was meewerkend in vergelyking met venlafaksien (38.8%) en duloksetien (38.7%). Verder het die studie bevind dat vroue ’n betekenisvolle verhoogde voorkoms van beide major depressiewe versteuring (MDV) en MIV/VIGS het in vergelyking met mans van dieselfde groep.

Die medemorbiditeit tussen MIV/VIGS en MDV het ’n betekenisvolle effek op AD pasiënt meewerkendheid. Pasiënte met beide MDV en MIV/VIGS MDD ( $74.43 \pm 32.03$ , 95%CI: 71.51-77.34) het ’n beduidende laer meewerkendheid in vergelyking met pasiënte wat slegs MDV ( $80.94 \pm 29.44$ , 95%CI: 80.56-81.33) onder lede het. Dit is opmerklik dat 75% ( $p < 0.0217$ ; Cramer’s  $V = 0.0388$ ) van alle venlafaksien pasiënte meewerkend was op hulle behandeling teenoor slegs 28.6% ( $p < 0.0197$ ; Cramer’s  $V = -0.0705$ ) van pasiënte wat meewerkend was op paroksetien in die groep pasiënte wat beide MDV en MIV/VIGS het.

Die oorhoofse meewerkendheid in die groep wat beide AD en GABAergiese (GDs) geneesmiddels gebruik het, was uiters laag (35.19% aanvaarbare meewerkendheid  $n = 42\ 869$ ). In die groep wat beide ADs en GDs geneem het is ’n verlengde behandelings tydperk ( $406.60$  dae 95%CI: 403.20 – 409.90 vs. 252.70 dae; 95%CI: 250.20 – 255.20) word geassosieer met ’n betekenisvolle ( $p < 0.0001$ ) verhoging in AD meewerkendheid. In die huidige studiegroep is amitriptilien (29.57%), mirtasepien (31.36%) en fluoksetien (32.29%) geassosieer met die swakste meewerkendheid terwyl duloksetien (40.67%) die hoogste meewerkendheid gehad het. Laastens, antidepressante met die laagste meewerkendheid word

geassosieer met verhoogde GDs verbruik. Alprazolam (n = 10 201) en zolpidem (n = 9 312) is die mees algemeenste groep GDs wat geresepteer is saam met AD.

In samevatting, die huidige studie bevestig dat AD meewerkendheid 'n geweldige struikelblok is vir die doeltreffende behandeling van MDV in beide ontwikkelende en ontwikkelde lande. Antidepressant nie-meewerkendheid het verrykende gevolge veral met die ontwikkeling van antidepressant onttrekkingsindroom wat die siektetoestand verder kompliseer en kan 'n voorloper wees vir die ontwikkeling van behandelingsweerstandige depressie. Die studie identifiseer 'n hele paar faktore wat 'n rol speel in behandelingsmeewerkendheid soos; die farmakologiese klas van AD, geslag, kroniese medemorbiditeit siektes en 'n verkorte behandelingstydperk.

**TREFWOORDE:** Antidepressante, geneesmiddelmeewerkendheid, antidepressant onttrekkingsindroom, medisyne besit verhouding, major depressiewe versteuring, Suid Afrika, halfleeftyd, anhedonie, angsversteuring, serotonientransporter, fase reseptor besetting, neuroplastisiteit, MIV/VIGS, venlafaksien, GABAergiese middels en behandelingweerstandige depressie.

## AUTHORS CONTRIBUTIONS

Article	Authors Contributions
<p>Article 3.1 New insights on the antidepressant discontinuation syndrome.</p>	<p>B. H. Harvey devised the concept and wrote the first draft of the manuscript.</p> <p>F. N. Slabbert co-wrote the pre-submission draft of the manuscript and did all the subsequent literature research for the final manuscript.</p> <p>Both authors prepared the final manuscript for publication.</p>
<p>Article 3.2 Prospective analysis of the Medicine Possession Ratio (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011)</p>	<p>F.N. Slabbert was involved in designing the study, the drafting of the manuscript, as well as performing the analysis and interpretation of data.</p> <p>M.S. Lubbe performed the statistical analysis with direct inputs from F.N. Slabbert.</p> <p>B.H. Harvey and C.B. Brink revised the manuscript and provided extensive intellectual inputs.</p> <p>All the authors were involved in the design of the study and the research methodology. All authors read and approved the final manuscript.</p>
<p>Article 3.3 Impact of HIV/AIDS on compliance to antidepressant treatment in major depressive disorder: A prospective study in a South African private health care cohort.</p>	<p>F.N. Slabbert was involved in designing the study, the drafting of the manuscript, as well as performing the analysis and interpretation of data.</p> <p>M.S. Lubbe performed the statistical analysis with direct inputs from F.N. Slabbert.</p> <p>B.H. Harvey and C.B. Brink revised the manuscript and provided extensive intellectual inputs.</p> <p>All the authors were involved in the design of the study and the research methodology. All authors read and approved the final manuscript.</p>
<p>Article 3.4 The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort.</p>	<p>F.N. Slabbert was involved in designing the study, the drafting of the manuscript, as well as performing the analysis and interpretation of data.</p> <p>M.S. Lubbe performed the statistical analysis with direct inputs from F.N. Slabbert.</p> <p>B.H. Harvey and C.B. Brink revised the manuscript</p>

	and provided extensive intellectual inputs.  All the authors were involved in the design of the study and the research methodology. All authors read and approved the final manuscript.
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Prof. B.H. Harvey

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Prof. C.B.Brink

## LIST OF ABBREVIATIONS

### A

AC	Adenylate Cyclase
ACC	Anterior Cingulate Cortex
Ach	Acetylcholine
AD	Antidepressant
ADS	Antidepressant Discontinuation Syndrome
ADs	Antidepressants
AIDS	Acquired Immune Deficiency Syndrome
AMPA	$\alpha$ -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
APA	American Psychiatric Association

### B

BDNF	Brain Derived Neurotrophic Factor
BZDs	Benzodiazepines

### C

CAD	Coronary Artery Disease
cAMP	Cyclic Adenosine 3',5'-Monophosphate
CANMAT	Canadian Network for Mood and Anxiety Treatments
cART	Combination Antiretroviral Therapy
CD4	Cluster of Differentiation 4
cGMP	Cyclic Guanosine 3',5'-Monophosphate
CI	Confidence Interval
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CREB	cAMP Response Element-Binding Protein
CRH	Corticotropin-Releasing Hormone

CRHBP	Corticotropin-Releasing Factor-Binding Protein
D	
D <sub>2</sub>	Dopamine 2 receptor
DA	Dopamine
DDD	Defined Daily Dosage
DLFPC	Dorsolateral Prefrontal Cortex
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders
E	
e.g.	Example
ECG	Electrocardiography
Etc.	Etcetera
F	
FC	Frontal Cortex
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FSL	Flinder Sensitive Line
G	
GABA	γ-Aminobutyric Acid
GAD	Generalized Anxiety Disorder
GC	Guanylyl Cyclase
GD	Gabaergic Drug
GDs	Gabaergic Drugs
GPCRs	G Protein-Coupled Receptors
GR	Glucocorticoid Receptors
GSRD	European Group for the Study of Resistant Depression
H	
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal

HPC	Hippocampus
HPCSA	Health Professionals Council of South Africa
I	
i.e.	In Other Words
ICD-10	International Classification of Diseases – 10
IFN- $\alpha$	Interferon Alpha
IL-1	Interleukin 1
IL-1 $\beta$	Interleukin 1 Beta
IL-6	Interleukin 6
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LOPFC	Lateral Orbital Prefrontal Cortex
M	
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
MAOIs	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MIMS	Monthly Index of Medical Specialities
MOA-A	Monoamine Oxidase A
mPFC	Medial Prefrontal Cortex
MPR	Medicine Possession Ratio
MT <sub>1</sub>	Melatonin 1 Receptor
MT <sub>2</sub>	Melatonin 2 Receptor
N	
NA	Noradrenaline
NAPPI	National Pharmaceutical Product Index
NASSA	Noradrenergic and Specific Serotonergic Antidepressant
NET	Noradrenaline Transporter

NICE	National Institute for Health and Care Excellence
NMDA	N-Methyl-D-aspartate
NO	Nitric Oxide
NT-3	Neurotrophin-3
O	
OR	Odds Ratio
OTC	Over The Counter
P	
PBM	Pharmaceutical Benefit Management
PDD	Prescribed Daily Dose
PFC	Prefrontal Cortex
R	
RNA	Ribonucleic Acid
S	
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SERT	Serotonin Reuptake Transporter
SN	Substantia Nigra
SNP	Single Nucleotide Polymorphism
SNRIs	Serotonin Noradrenalin Reuptake Inhibitors
SRI	Serotonin Reuptake Inhibitor
SSRIs	Selective Serotonin Reuptake Inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
T	
T <sub>½</sub>	Half-Life
T <sub>4</sub>	Thyroxine
TCAs	Tricyclic Antidepressants
TNF α	Tumor Necrosis Factor alpha

TRD	Treatment Resistant Depression
TREK1	Potassium channel subfamily K member 2
TRkB	Tyrosine Receptor Kinase Receptor
U	
UK	United Kingdom
UNAIDS	United Nations Program on HIV/AIDS
USA	United States of America
V	
VMPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area
W	
WHO	World Health Organisation
WFSBP	World Federation of Societies of Biological Psychiatry
X	
XR	Extended Release
$\chi^2$	Chi Square
5-HT	Serotonin
5-HT <sub>1A</sub>	Serotonin 1A Receptor
5-HT <sub>2c</sub>	Serotonin 2C Receptor
5-HTT	Serotonin Transporter
5-HTTLPR	Serotonin-Transporter-Linked Polymorphic Region

# TABLE OF CONTENTS

<b>PREFACE</b>	<b>I</b>
<b>ACKNOWLEDGEMENTS</b> .....	<b>II</b>
<b>ABSTRACT AND KEYWORDS</b> .....	<b>III</b>
<b>UITTREKSEL EN TREFWOORDE</b> .....	<b>V</b>
<b>AUTHORS CONTRIBUTIONS</b> .....	<b>VII</b>
<b>LIST OF ABBREVIATIONS</b> .....	<b>IX</b>
<b>CHAPTER 1: STUDY OVERVIEW AND BACKGROUND</b> .....	<b>1</b>
<b>1.1 Introduction</b> .....	<b>1</b>
<b>1.2 Background</b> .....	<b>1</b>
<b>1.3 Research questions</b> .....	<b>4</b>
<b>1.4 Research aim and specific research objectives</b> .....	<b>5</b>
1.4.1 Research aim .....	5
1.4.2 Specific literature objectives .....	5
1.4.3 Specific empirical research objectives .....	5
<b>1.5 Research methodology</b> .....	<b>6</b>
1.5.1 Pharmacoepidemiology .....	6
1.5.2 Empirical investigation .....	7
1.5.3 Research design .....	7
1.5.4 Data source .....	7
1.5.5 Target population .....	8
1.5.6 Study population .....	8
1.5.7 Study variables .....	11
1.5.8 Data analysis .....	14

1.6	<b>Ethical considerations</b> .....	16
1.7	<b>Value of the current thesis</b> .....	16
1.8	<b>Chapter summary and outline of the study</b> .....	16
<b>CHAPTER 2: LITERATURE STUDY</b> .....		<b>18</b>
2.1	<b>Introduction</b> .....	<b>18</b>
2.2	<b>Epidemiology of major depression disorder (MDD)</b> .....	<b>18</b>
2.2.1	Prevalence of MDD.....	18
2.2.2	Onset of MDD .....	20
2.2.3	The neurobiology of MDD.....	24
2.3	<b>Current treatment for MDD</b> .....	<b>33</b>
2.3.1	Selective serotonin reuptake inhibitors (SSRIs).....	34
2.3.2	Tricyclic Antidepressants (TCAs) .....	38
2.3.3	Monoamine oxidase inhibitors (MAOIs) .....	40
2.3.4	Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) .....	41
2.3.5	Other antidepressants .....	42
2.4	<b>Problems related to the use of antidepressant drugs</b> .....	<b>47</b>
2.4.1	Duration of AD treatment for depression.....	47
2.4.2	Treatment-resistant depression and tardive dysphoria.....	48
2.4.3	Antidepressant discontinuation syndrome .....	49
2.4.4	Co-prescribing of GABAergic drugs in MDD .....	49
2.4.5	Patient non-compliance .....	51
2.5	<b>Depression and co-morbid diseases</b> .....	<b>52</b>
2.5.1	Coronary artery disease and other cardiac disorders .....	52
2.5.2	Stroke.....	53
2.5.3	Obesity.....	54
2.5.4	Type 2 diabetes mellitus .....	54
2.6	<b>Neuropsychiatric manifestations and disorders</b> .....	<b>55</b>
2.6.1	Anxiety disorders associated with MDD .....	55

2.6.2	Dysthymic disorder .....	55
2.6.3	Dementia .....	56
2.6.4	Personality disorder .....	56
<b>2.7</b>	<b>Human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) and MDD .....</b>	<b>56</b>
<b>2.8</b>	<b>Synopsis .....</b>	<b>58</b>
 <b>CHAPTER 3: MANUSCRIPT 3.1.....</b>		<b>59</b>
<b>3.1</b>	<b>Article 1.....</b>	<b>60</b>
 <b>CHAPTER 3: MANUSCRIPT 3.2.....</b>		<b>74</b>
<b>3.2</b>	<b>Article 2.....</b>	<b>75</b>
 <b>CHAPTER 3: MANUSCRIPT 3.3.....</b>		<b>92</b>
<b>3.3</b>	<b>Article 3.....</b>	<b>92</b>
 <b>CHAPTER 3: MANUSCRIPT 3.4.....</b>		<b>111</b>
<b>3.4</b>	<b>Article 3.4.....</b>	<b>111</b>
 <b>CHAPTER 4: CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS.....</b>		<b>127</b>
<b>4.1</b>	<b>Conclusions and key findings deduced from the literature review .....</b>	<b>127</b>
4.1.1	New insights into antidepressant discontinuation syndrome .....	127
<b>4.2</b>	<b>Conclusions deduced from the empirical investigation.....</b>	<b>128</b>
4.2.1	Prospective analysis of the medicine possession rate (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011) .....	128
4.2.2	Impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private health care cohort .....	130
4.2.3	The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort.....	131
<b>4.3</b>	<b>Recommendations for future studies .....</b>	<b>133</b>
<b>4.4</b>	<b>Limitations of the current study .....</b>	<b>134</b>

<b>REFERENCES.....</b>	<b>136</b>
<b>ADDENDUM 1: HUMAN PSYCHOPHARMACOLOGY: CLINICAL AND EXPERIMENTAL .....</b>	<b>187</b>
<b>ADDENDUM 2: SOUTH AFRICAN MEDICAL JOURNAL.....</b>	<b>193</b>
<b>ADDENDUM 3: AIDS RESEARCH AND THERAPY.....</b>	<b>198</b>
<b>ADDENDUM 4: BMC PSYCHIATRY .....</b>	<b>210</b>
<b>ADDENDUM 5: APPROVAL OF ARTICLE 2 .....</b>	<b>223</b>
<b>ADDENDUM 6: APPROVAL OF ARTICLE 3 .....</b>	<b>224</b>

## LIST OF TABLES

Table 1.1:	Specific research objectives according to the presented scientific research articles.....	5
Table 1.2:	A detailed description of the study population.....	8
Table 1.3:	A summary of the different samples obtained.....	11
Table 2.1:	Antidepressants registered for the treatment of MDD in adults in South Africa according to Monthly Index of Medical Specialities (Snyman, 2012).....	33
Table 2.2:	Half-life ( $T_{1/2}$ ) of selected antidepressants .....	37

## LIST OF FIGURES

Figure 2.1:	Anatomy of the human brain in three different views; lateral, coronal and midsagittal. The function of this illustration is to indicate the different parts of the brain affected by MDD as discussed in the text and also serves as a guide to the reader to show where the different brain structures associated with MDD are positioned in the brain (Lane et al., 2009).....	26
Figure 2.2:	Inflammatory and neurodegenerative pathways in depression. The molecular changes associated with MDD. (1) Indicates the impaired regulation of the HPA axis, (2) the proinflammatory cytokines that play a role in the weakening of neurotrophic support and monoamine neurotransmission, (3) the decrease in neurotrophic factors such as BDNF that leads to a decrease in neurogenesis and (4) the structural changes seen in the hippocampus, PFC and the amygdala due to neurodegeneration. This figure was adapted from (Harvey, 2008; Maes et al., 2009).....	28
Figure 2.3:	Schematic representation of glutamatergic neurotransmission. After the release of glutamate from the presynaptic terminal, glutamate binds to various receptors, including ionotropic (AMPA and NMDA) and metabotropic glutamate receptors. Glutamate is terminated from the synapse via the reuptake mechanism mediated by the glutamate transporter located on the presynaptic terminal as well as on astrocytes (Carlson et al., 2006).....	31
Figure 2.4:	The mechanism of action of the SSRIs. 5-HT is released from the terminal vesicle after which it binds to 5-HT receptors. In depression, there is a decrease in the synaptic 5-HT concentration. The SSRI binds to the 5-HTT in order to decrease the reuptake of 5-HT from the synaptic cleft and therefore increases the concentration of 5-HT in the synaptic cleft, resulting in an increased activation of postsynaptic 5-HT receptors (Adapted from CNSforum, 2011).....	35
Figure 2.5:	The mechanism of action of the TCAs is illustrated. The TCAs bind to the 5-HT and NA reuptake transporters presynaptically to increase the amount of monoamines in the synaptic cleft. In this figure, the amount of histamine is shown to increase due the blockade of histamine receptors, which is associated with sedation as a side effect of the TCAs. Furthermore, the blockade of muscarinic and $\alpha$ adrenergic receptors is also associated with the side effects experienced by patients (adapted from CNSforum, 2011).....	38
Figure 2.6:	The mechanism of action of the SNRIs. The SNRI class of ADs blocks both the 5-HT and NA reuptake transporter in order to increase the total amount of monoamine in the synaptic cleft and to restore the monoamine balance (adapted from CNSforum, 2011).....	42

Figure 2.7:	The mechanism of action of mirtazapine. Mirtazapine has a dual mechanism of action that increases the concentration of 5-HT and noradrenaline in the synaptic cleft. NASSAs bind to and inhibit both noradrenaline $\alpha$ 2-autoreceptors and noradrenaline $\alpha$ 2-heteroreceptors. This action prevents the negative feedback effect of synaptic noradrenaline on 5-HT and noradrenaline neurotransmission, and neurotransmission sustained. NaSSAs also block 5-HT2 and 5-HT3 receptors on the post-synaptic membrane, which causes enhanced 5-HT1-mediated neurotransmission (CNSforum, 2011).....	44
Figure 2.8:	Illustration of the effect of chronic agomelatine treatment on the monoaminergic system. . (1) After 14 days, agomelatine induces an excitatory effect on DA cells in the ventral tegmental area (VTA), (2) causing an increase in DA neurotransmission (3) leading to the activation of excitatory D2 receptors. (4) An increase in 5-HT firing (5) induces the activation of excitatory 5-HT2A receptors in the GABA interneurons. (6) The increase in GABA activity inhibits the locus coeruleus noradrenaline (LC-NA) neurons. (7) Acute agomelatine (2 days) treatment also exerts an excitatory effect on the LC-NA neurons. The (4) increase in 5-HT firing induces the (9) activation of inhibitory postsynaptic 5-HT1A receptors that may contribute to a decrease in the hyperactivity of the hippocampus frequently detected in MDD patients (Chenu et al., 2013).....	46
Figure 2.9:	A schematic illustration of the treatment and phases of MDD (Bauer et al., 2013) .....	47
Figure 2.10:	Compliance is calculated over a period of time from the start of therapy until the end of the observation period and is expressed as a percentage (%) (Cramer <i>et al.</i> , 2008).....	51

# CHAPTER 1: STUDY OVERVIEW AND BACKGROUND

## 1.1 Introduction

This is the first prospective cohort study undertaken in the private health sector of South Africa that will concentrate on antidepressant (AD) treatment compliance by using medicine claims data. The compliance will be calculated using the medication possession ratio (MPR), which is a recognised method used in prospective studies. Furthermore, the international classification of disease version 10 (ICD-10) codes will be used to isolate all major depression disorder (MDD) (F32) patients diagnosed by a psychiatrist. In patients who are non-compliant, we will endeavour to identify possible consequences of non-compliance, such as the influence of the prescribed daily dosage on AD treatment compliance. In addition, an in-depth literature review will be conducted looking at the underlying neurobiology and the clinical consequences of non-compliance. South Africa is one of the countries hardest hit by the HIV/AIDS pandemic, with devastating effects on the country as well as the individual living with HIV/AIDS. In the empirical study, we will look into the association between MDD and HIV/AIDS and how this co-morbidity affects AD compliance in the treatment of MDD. MDD is closely associated with co-morbid anxiety. The co-morbid anxiety might be responsible for the high failure rates during the initial treatment phase that lead to antidepressant non-compliance. Therefore the current study will focus on the GABAergic drugs with the focus on anxiolytics and sedative hypnotics such as the benzodiazepines, zolpidem and zopiclone. The study will investigate the influence of GABAergic drugs on the AD treatment compliance.

## 1.2 Background

Mood disorders (MDD, dysthymia, bipolar disorder I and II) are among the most prevalent forms of mental illness. A study performed in the United States (Kessler *et al.*, 2005) reported that 16.7% of the total population will develop clinical depression at some stage during their lifetime. The World Health Organization (WHO) (2009) projects that MDD will by 2020 become the second most debilitating disease across all age groups.

Depression is a serious psychiatric disorder that is associated with a great degree of suffering, as well as being a major cause of suicide (i.e. relatively high mortality), with a reported one million lives being claimed worldwide by suicide each year (WHO, 2012). In addition, depressed patients are also more likely to develop a cardiovascular disease (Halaris, 2009) and type 2 diabetes (Knol *et al.*, 2006), whereas MDD complicates the prognosis of several other chronic illnesses, foremost among these being cardio-metabolic disorders such as coronary artery disease, metabolic syndrome, obesity etc. (Gildengers *et al.*, 2008; Evans *et al.*, 2005). It is sobering to note that a lifetime prevalence of 9.7% has been reported for MDD in the South African population (Tomlinson *et al.*, 2009). Ciesla and Roberts (2001) found that the frequency of MDD was nearly twice as high in HIV-positive subjects as in the HIV-negative control group (Ciesla & Roberts, 2001). In addition, the prevalence of HIV/AIDS in South Africa further contributes to the incidence of MDD (Owe-Larsson *et al.*, 2009). This is triggered by the emotional trauma and stigmatisation that HIV-positive patients commonly experience, and is further complicated by the occurrence of antiretroviral drug-related side-effects and the neurocognitive complications associated with HIV/AIDS and its treatment (Owe-Larsson *et al.*, 2009).

In the treatment of MDD, drug non-compliance or non-persistence is an established problem. Several studies suggest that up to 30% of patients stop taking antidepressants within the first month after the

initiation of treatment and 45 to 60% stop their prescribed treatment by the end of the third month (Hotopf *et al.*, 1997; Lin *et al.*, 1995, Robinson *et al.*, 1995). Several studies have demonstrated that non-compliance with antidepressants results in increased morbidity and mortality (Akerblad *et al.*, 2008, Taylor *et al.*, 2006, Warner *et al.*, 2006). Non-compliant behaviour includes premature or temporary discontinuation of medication as well as incorrect usage of medication, and changes in dose regimes without the knowledge of the prescriber (Akerblad *et al.*, 2008). Although antidepressants are at best 50 to 55% effective (Rush *et al.*, 2004), non-compliance with current treatment regimens can worsen the scenario, which poses significant clinical obstacles (Hansen *et al.*, 2010). Non-compliance undermines the optimal treatment of depressive disorders and increases the risk of suicide (Meehan *et al.*, 2006). Moreover, without adequate treatment, patients will experience further relapses and depressive episodes (Frank *et al.*, 1990), while there is evidence in the preclinical literature that inappropriate discontinuation may evoke a specific sequence of neurobiological events that underlie relapse and treatment resistance (Harvey *et al.*, 2002, Harvey *et al.*, 2003, Harvey *et al.*, 2006).

The process of medication compliance begins with an appointment with a relevant clinician, followed by the submission of a prescription to a pharmacy, acquisition of the drugs and correct and appropriate medication consumption (Steiner & Prochazka, 1997). Clinicians have long been aware of the importance of long-term compliance with antidepressant treatment (Keller & Boland, 1998). Despite such knowledge, patients with MDD and anxiety disorders often tend to discontinue their treatment prematurely (Scott, 2001). Among the reasonable causes of premature antidepressant discontinuation, is the poor tolerability of the older generation antidepressants. However, since the introduction of novel antidepressants, such as the SSRIs and the new generation drugs such as agomelatine, this issue has to a large extent been addressed (Anderson, 2000; Demyttenaere, 2011). Possibly more important is the fact that the premature discontinuation of antidepressant treatment may result from a lack of knowledge concerning the neurobiological mechanisms underlying depression and the implications of antidepressant withdrawal on the progress and prognosis of MDD (Harvey *et al.*, 2003).

Interruption of antidepressant treatment is sometimes associated with an antidepressant discontinuation syndrome (ADS). Antidepressant discontinuation syndrome has been associated with all classes of antidepressants, including the tricyclic antidepressants, (TADs) (Garner *et al.*, 1993), monoamine oxidase inhibitors (MAOIs) (Dilsaver, 1994), selective serotonin reuptake inhibitors (SSRIs) (Haddad, 1998) and serotonin-noradrenalin reuptake inhibitors (SNRIs) (Taylor *et al.*, 2006). Typical symptoms of ADS include flu-like symptoms, insomnia, physical imbalance, sensory disturbances and hyper-arousal (Warner *et al.*, 2006). The pharmacokinetic properties of these drugs, such as plasma half-life, clearance rate and molar potency for reuptake inhibition, may be partly responsible for the frequency and eventual effects of the ADS (Schatzberg *et al.*, 1997).

Although sustained long-term antidepressant treatment is a prerequisite to maximise successful remission of the illness (Harvey, 1997; Harvey *et al.*, 2003), evidence suggests that the incorrect and inappropriate long-term use of antidepressants may enhance the biochemical vulnerability to MDD and worsen its long-term outcome (Fava & Offidani, 2011). In this scenario, inappropriate use refers to the long-term 'abuse' of antidepressants, which is generally associated with the inadequate management of the illness, and includes recurrent non-compliance, switching between antidepressants of different classes and long-term drug administration at sub-therapeutic levels. Subsequently, the worsening of long-term treatment outcomes has been referred to as tolerance and may decrease both the likelihood of future response to pharmacological treatment and the duration of symptom-free periods (Fava & Offidani, 2011). Indeed, antidepressants may induce adverse events such as withdrawal symptoms

upon treatment discontinuation, leading to the onset of tolerance and the resistance phenomena (Fava & Offidani, 2011). In the current research project, we will evaluate patients who have used antidepressants chronically for up to six years and who are compliant with their current treatment, looking specifically at the relevant medication history as a means to determine whether the patient's condition has improved or not. The project will therefore investigate whether certain trends are evident in the prescription history that may indicate whether a patient is compliant and whether the medication record for each patient can be associated with any evidence of clinical improvement or not (Bulloch & Patten, 2010; Milea *et al.*, 2010, Sawada *et al.*, 2009). Treatment resistance in MDD appears to be increasing. The fact that antidepressants may lose efficacy over time (antidepressant tachyphylaxis) goes hand-in-hand with evidence suggesting that in some individuals the persistent use of antidepressants may be pro-depressant (El-Mallakh *et al.*, 2011). Treatment resistance is frequently preceded by an initial positive clinical response to an antidepressant. Treatment resistance usually occurs in individuals who have used these antidepressant agents for a long period of time at a very high dosage. This phenomenon has been linked to tardive dyskinesia and is referred to as tardive dysphoria (El-Mallakh *et al.*, 2011). Some authors have associated this form of drug resistance specifically with the TCAs (van Scheyen, 1973; Di Mascio *et al.*, 1968). In the current research project, we will analyse the long-term medication use of patients and the different types of antidepressants being used.

The complex nature of MDD, particularly the variable presence of a number of symptoms as well as comorbid disorders related to sleep and anxiety often necessitates the need for co-prescribing of other classes of psychotropic together with the AD (Huedo-Medina *et al.*, 2012). Moreover, side effects associated with some ADs, such as anxiety and insomnia with SSRI's, also often prompts co-prescribing (Edwards & Anderson, 1999). Drugs acting on  $\gamma$ -amino-butyric acid (GABA) signalling, otherwise referred to as GABAergics (e.g. benzodiazepines, zolpidem and zopiclone) are currently the most widely prescribed psychotropic drugs world-wide (Huedo-Medina *et al.*, 2012). The co-morbidity between anxiety disorders and depression is approximately 50 – 60% (Kaufman & Charney, 2000; Meijer *et al.*, 2004; Sanyal *et al.*, 2011). The benzodiazepines are closely associated with adverse effects such as dependence, discontinuation withdrawal and impaired cognition that ultimately limit their efficacy (Valenstein *et al.*, 2004). However, benzodiazepines are suggested to be advantageous during the initial treatment phase (two to four weeks) of MDD as it has a faster onset of action and thus reduces anxiety related symptoms associated with both MDD and AD induced anxiogenic effects (Birkenhager *et al.*, 1995; Edwards & Anderson, 1999; Howard *et al.*, 2014; Outhoff, 2010). Importantly, benzodiazepines have been found to increase AD treatment compliance during the first weeks of treatment compared to patients taking ADs alone and to reduce dropout rates, but after six to twelve weeks benzodiazepine effects on AD treatment dropout diminished significantly (Furukawa *et al.*, 2001).

A number of concepts have been defined that have proven to be valuable for medicine utilisation research. Medicine compliance refers to the act of conforming to the recommendations made by the healthcare provider with respect to the timing, dosage and frequency of medicating (Cramer *et al.*, 2008b). When applied in prospective studies, the number of doses dispensed in relation to the dispensed period is often also called the medication possession ratio (MPR). The MPR is defined as the number of days for which medication is supplied within the refill interval (medicine treatment period) divided by the number of days in the refill interval (Paterson *et al.*, 2000:25; Steiner *et al.*, 1997:108; Stein, 2012). Sawada *et al.* (2009) conducted one of the first studies to simultaneously distinguish between the two concepts of compliance and persistence in a clinical outpatient setting (Sawada *et al.*, 2009). This study was also conducted in depressed patients looking at antidepressant utilisation. However, this latter study has some drawbacks. Firstly, it was only conducted on 367 outpatients,

which, in retrospect, may have been too few to make conclusive suggestions, and secondly, the study was only conducted over a period of one year, while the recommended treatment period for depression is at least two years (NICE, 2009).

Gilat and co-workers (2011) examined the prescribing trends for psychotropic drugs in a 10-year retrospective analysis in depressed inpatient adolescents in a psychiatric ward (Gilat *et al.*, 2011). Over the 10-year duration of the study, they found a significant increase in the number of psychotropic drugs dispensed per patient at discharge, as well as a significant increase in the number of patients who received psychotropic drugs. However, what is important to note is that the study by Gilat *et al.* (2009), in addition to its emphasis on antidepressants, also focused on other psychotropic drugs, and therefore followed a similar protocol as the current proposed study. In contrast to the study by Sawada *et al.* (2009), this study was conducted over a period of 10 years, allowing for clear and accurate conclusions to be made. On the other hand, such a controlled setting in a psychiatric hospital is not necessarily a realistic reflection of the naturalistic setting. In fact, in an uncontrolled setting, after the medication has been supplied, it is subject to individual patterns of usage. The study of Gilat *et al.* (2011) only focused on the different classes of drugs dispensed and did not investigate either compliance or persistence.

The present study builds on much of the aforementioned studies, but will offer a number of unique opportunities, namely to investigate the current trends in the treatment regimens for MDD in the private health sector of South Africa (see articles 3.3 and 3.4). The study will be an improvement on existing studies in that it offers new data on the drug utilisation trends of the past six years, from 1 January 2006 to 31 December 2011, from which an individual's total drug profile (based on medical aid claims) can be traced. More importantly, the data will provide us with an accurate tool to evaluate whether or not a patient has been compliant or not.

### **1.3 Research questions**

The following research questions were formulated for this study, namely:

- Review the current evidence regarding the development of ADS and the role that non-compliance to antidepressant treatment plays in this syndrome.
- What is the relation between antidepressant treatment non-compliance and the development of ADS?
- What is the average compliance rate to antidepressant treatment in the private health sector of South Africa?
- How does compliance and non-compliance with antidepressant treatment affect the PDD of antidepressants?
- What is the prevalence of MDD patients in South Africa also living with HIV/AIDS?
- How does MDD affect antidepressant compliance in HIV/AIDS-positive patients in South Africa?
- Is there any association between gender and antidepressant compliance?
- Which antidepressant is associated with the best treatment compliance in MDD patients living with HIV/AIDS?

- What is the influence of GABAergic drugs on AD compliance?
- Which antidepressants are more associated with non-compliance in combination with GABAergic drugs?
- Which GABAergic drugs are most frequently dispensed with ADs?

#### 1.4 Research aim and specific research objectives

##### 1.4.1 Research aim

The main aim of the current research study is to establish a viable method to investigate AD treatment compliance in such a manner that meaningful clinical pharmacological assumptions can be formulated.

##### 1.4.2 Specific literature objectives

In order to better formulate and design the research study, specific objectives for the literature review were set, and include the following:

- To determine the prevalence of MDD globally as well as in South Africa.
- To conceptualise the latest discoveries regarding the onset and development of MDD with regard to the neuro-pathophysiology.
- To determine the current MDD treatments available in South Africa, the mechanism of action and a comprehensive adverse effect profile of these antidepressants.
- To identify those co-morbid illnesses closely associated with MDD.
- To review the current literature regarding the neurobiological and clinical consequences as a result non-compliance with antidepressant treatment and the resulting ADS.
- To review the latest class of antidepressant, agomelatine, which is now reported not be associated with ADS, following discontinuation, will be staged as a counterpoint in order to determine the role of pharmacology and pharmacokinetics in the development of ADS.

##### 1.4.3 Specific empirical research objectives

The specific empirical objectives are provided in Table 1, with the corresponding article in which this outcome is achieved.

**Table 1.1: Specific research objectives according to the presented scientific research articles**

Articles (refer to chapter 3)	Specific research objectives
Article 3.1 Harvey, B.H. & Slabbert, F.N. 2014. New insights on the antidepressant discontinuation syndrome. Human Psychopharmacology: Clinical and Experimental. Published online. DOI: 10.1002/hup.2429	Write a review on the current literature regarding the neurobiological and clinical consequences following non-compliance with antidepressant treatment and the resulting ADS.  The latest class of antidepressant, agomelatine, known to not induce ADS, will be staged as a counterpoint in order to determine the role of

Articles (refer to chapter 3)	Specific research objectives
	pharmacology and pharmacokinetics in the development of ADS.
<p>Article 3.2 Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. Prospective analysis of the Medicine Possession Rate (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011). South African Medical Journal. Published online. DOI:10.7196/SAMJ.8394</p>	<p>To establish an estimate prevalence of non-compliance with antidepressant use in the private health sector of South Africa. Furthermore, this article will be used to establish the method and its validity for use in the subsequent studies.</p> <p>To determine a possible change in prescribed daily dosage (PDD) between compliant and non-complaint individuals on AD treatment.</p> <p>To establish the influence of gender, age and AD class on the compliance with antidepressant treatment.</p>
<p>Article 3.3 Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. The impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private healthcare cohort. (Accepted for publication).</p>	<p>To determine the prevalence of the prevalence of HIV/AIDS-positive patients within the MDD-diagnosed population in the private health sector of South Africa.</p> <p>To determine the possible effect of both illnesses (MDD and HIV/AIDS positive) on antidepressant compliance.</p>
<p>Article 3.4 Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort. BioMed Central Psychiatry. (To be submitted for peer review).</p>	<p>To determine the influence of co-prescribed GDs on AD treatment compliance and vice versa.</p> <p>This study will investigate the GDs additionally prescribed to MDD patients, although not necessarily intended as a bona fide augmentation strategy for TRD</p> <p>This study will also determine which ADs are associated with the worst compliance in combination with GDs.</p> <p>Is there is a link between AD treatment compliance and the use of GDs.</p>

## 1.5 Research methodology

In the following section, the research methodology used in the current study will be described in detail.

### 1.5.1 Pharmacoepidemiology

Pharmacoepidemiology is the study of the uses and effects of drugs in well-defined populations. In order to undertake such a study, one uses both pharmacologic (e.g. pharmacodynamics, therapeutic outcomes and to a limited extent pharmacokinetics) and epidemiologic (e.g. case-control studies, cohort studies and randomized trials) principles (Van Boxtel & Wang, 1997; Strom, 1994; Martin, 2005) as a means to address certain research questions. Pharmacoepidemiology plays an important role in documenting and understanding the complex relationship between the use of medication and adverse effects and its influence on treatment outcome (Kaufman, 2008). In the current study, pharmacoepidemiology was an important tool in order to determine the association between antidepressant use and an individual's compliance with treatment.

### **1.5.2 Empirical investigation**

The empirical investigation for this thesis was done in the following phases:

- Selection of the research designs.
- Study populations and data extraction from data sources.
- Inclusion criteria and statistical analysis.
- Data analysis.
- Reliability and validity of the research instruments.
- Ethical aspects.
- Write research manuscripts reporting results, discussion and conclusions.
- Conclusions and recommendations based on the results described in the research manuscripts and also a summary of the limitations of the current study.

### **1.5.3 Research design**

The relevant literature study will be done through a MEDLINE search via PubMed, focusing on agomelatine and clinical and preclinical research on ADS, using keywords such as: compliance, non-compliance, neuropathophysiology, antidepressants, antidepressant discontinuation syndrome, inappropriate antidepressant usage, agomelatine, half-life, anhedonia, anxiety, serotonin transporter, phasic receptor occupancy, and neuroplasticity. Some of the literature objectives will be achieved through the first article (see 3.1).

Research articles 3.2, 3.3 and 3.4 will all follow an observational, prospective, cohort study. An observational study can be defined as a wide range of study designs including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies (Yang *et al.*, 2010). It has been proven that a well-designed observational study can provide comparable results to that of randomised control experiments (Song & Chang, 2010). Furthermore, cohort studies are considered to be one of the primary types of observational studies that can be utilised in evaluating disease and exposure to the drug (Song & Chang, 2010). Lastly a prospective cohort study can be define as a study that follows a group of individuals with similar characteristics (cohort) but differ by a certain characteristic (for example, patients diagnosed with MDD with or without co-prescribed psychotropic drugs) and compares how these different factors affect them for a particular outcome (such as treatment compliance) (National Cancer Institute, 2014).

### **1.5.4 Data source**

Of the total South African population of about 53-million, approximately 9.7-million people (~18.4%) are beneficiaries of private healthcare (Statistics South Africa, 2014), which is generally delivered through medical schemes. Medical schemes are the main way of financing private healthcare.

The data for the empirical investigation of this study were obtained from a national representative Pharmaceutical Benefit Management (PBM) company of South Africa. The company, from which the data were obtained, cannot be named because of ethical, security, patient and provider identification

reasons. Furthermore, it is an independent and specialist pharmaceutical benefit management organisation that provides real-time electronic pharmaceutical claims processing services to more than 1.5 million patients and 35 medical schemes. The PBM are at present linked up to all of South Africa's pharmacies and 98% of all dispensing doctors. The PBM's database currently contains longitudinal patient medicine claims data for more than 1.6 million medical scheme beneficiaries. The data acquired for this study covered a six-year period starting on 1 January 2006 to 31 December 2011.

The only information that will be extracted from the database includes the drug's trade name, the National Pharmaceutical Product Interface (NAPPI)-code, the date the prescription was filled, prescription number, patient dependant-, encrypted physician-, pharmacy- and medical scheme identification numbers, the number of the medicine items prescribed, number of days supplied, patient's gender, patient's date of birth, ICD-10 code for PMB chronic disease list conditions, patient's treatment date. No individual patient, medical scheme or health plan can or will be identified, thus ensuring confidentiality of the information and maintenance thereof.

#### 1.5.4.1 Reliability and validity of the data source

With the use of medicine claims data, two major problems can arise that have a direct influence on the reliability of data. Firstly, the quality of the data included in the database, and secondly, the ability of the analysis of non-experimental data to present valid results (Motheral & Fairman, 1997; Tannen *et al.*, 2009). The PBM Company that provided the data has the following validation processes in place to ensure the reliability and validity of the data: eligibility services, clinical management services, gate-keeping services, utilisation management services and price management along with real-time benefit management. These validation measures guarantee that the data used in this study met the required standards.

#### 1.5.5 Target population

The target population for this research thesis included all patients, on medical schemes, diagnosed with MDD with the same beneficiary profile within the South African private health sector.

#### 1.5.6 Study population

Table 2 describes the study population that was used in each of the last three manuscripts, with the first manuscript being a literature study.

**Table 1.2: A detailed description of the study population**

Article in which the described study population was used	Study population.
<p>Article 3.2 Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. Prospective analysis of the Medicine Possession Rate (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011). <i>South African Medical Journal</i>. Published online. DOI:10.7196/SAMJ.8394</p>	<p>A study population was selected according to the inclusion/exclusion criteria described below. The ICD-10 codes are based on the International Classification of Diseases, 10<sup>th</sup> edition published by the World Health Organization (WHO). In this study, the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist. Thereby, it was ensured that data were excluded where antidepressants may have been used for other</p>

Article in which the described study population was used	Study population.
	<p>illnesses, such as amitriptyline used for the treatment of chronic pain.</p> <p>The following inclusion criteria were applied:</p> <p>All patients who received antidepressant treatment between 2006 and 2011.</p> <p>Patients who received more than one antidepressant prescription.</p> <p>Patients who met the ICD-10 diagnose criteria of F32 and F33.</p> <p>Patients on antidepressant treatment for longer than 120 days.</p> <p>Only patients treated and diagnosed by a psychiatrist.</p> <p>All patients who were 18 years of age and older.</p> <p>The following exclusion criteria were applied:</p> <p>Patients who received only one prescription for antidepressant treatment.</p> <p>All individuals younger than the age of 18 years.</p> <p>Patients treated by any other prescriber than a psychiatrist.</p>
<p>Article 3.3.</p> <p>Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. Impact of HIV/AIDS on compliance to antidepressant treatment in major depressive disorder: A prospective study in a South African private health care cohort. AIDS Research and Therapy. (Accepted for publication).</p>	<p>The study population used in this research article included all patients diagnosed with MDD and all patients receiving HIV/AIDS prescriptions (antiretroviral drug). Additionally, the authors also studied MDD patients with co-morbid HIV/AIDS. The inclusion criteria are described in detail below. The ICD-10 codes are based on the International Classification of Diseases, 10<sup>th</sup> edition published by the World Health Organization. In this study, the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist, as well as B20-B24 (Human immunodeficiency virus [HIV/AIDS] disease), and all patients on cARV treatment.</p> <p>The following inclusion criteria were applied:</p> <p>All patients who received antidepressant treatment between 2006 and 2011.</p> <p>Patients who received more than one antidepressant prescription.</p> <p>Patients who met the ICD-10 diagnosis criteria of F32 and F33.</p> <p>The ICD-10 code for HIV/AIDS B20-24 was used as well.</p> <p>Patients on antidepressant treatment for longer than 120 days.</p> <p>All patients using combination antiretroviral therapy</p>

Article in which the described study population was used	Study population.
	<p>(cART).</p> <p>Only patients treated and diagnosed by a psychiatrist.</p> <p>All patients who were 18 years of age and older.</p> <p>The following exclusion criteria were applied:</p> <p>Patients who received only one prescription for antidepressant treatment.</p> <p>Patients who received only one prescription for antiretroviral drugs. All individuals younger than the age of 18 years.</p> <p>Patients treated by any other prescriber than a psychiatrist.</p>
<p>Article 3.4.</p> <p>Slabbert, F.N., Harvey, B.H., Brink, C.B. &amp; Lubbe, M.S. 2014. The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort. BioMed Central Psychiatry. (To be submitted for peer review).</p>	<p>All patients included in this study were older than 18 years of age and were diagnosed with MDD by a psychiatrist supported by the correct ICD-10 code based on the International Classification of Diseases, 10<sup>th</sup> edition published by the World Health Organization. In this study, the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist. This current study used the South African based MIMS classification (1.2 sedative hypnotics and 1.3 anxiolytics) to identify the GABAergic drugs used in MDD to treat co-morbid anxiety and insomnia.</p> <p>The following inclusion criteria were applied:</p> <p>All patients who received antidepressant treatment between 2006 and 2011.</p> <p>Patients who received more than one antidepressant prescription.</p> <p>Patients who met the ICD-10 diagnosis criteria of F32 and F33.</p> <p>Only patients treated and diagnosed by a psychiatrist.</p> <p>Patients on antidepressant treatment for longer than 120 days.</p> <p>All patients who were 18 years of age and older.</p> <p>Patients using the following psychotropic drugs were also included. The psychotropic drugs included in this study are associated with improving mood and reduce MDD symptomology when co-prescribed with ADs.</p> <p>Sedative hypnotics</p> <p>Anxiolytics</p> <p>Antidepressants</p> <p>The following exclusion criteria were applied:</p> <p>Patients who received only one prescription for</p>

Article in which the described study population was used	Study population.
	antidepressant treatment. All individuals younger than the age of 18 years. Patients treated by any other prescriber than a psychiatrist. Patients using any other psychotropic drug than those mentioned above were excluded from the current study.

### 1.5.6.1 Description and verification of sample size

Table 3 illustrates the sample sizes that were used in each of the manuscripts

**Table 1.3: A summary of the different samples obtained**

Description of the sample	Sample size (n)
Article 3.2	
Total number of patients diagnosed with MDD	14 285
Total number of dispensed items	35 175
Number of items associated with acceptable compliance	12 049
Number of items associated with unacceptable compliance	23 126
Article 3.3	
Total number of patients diagnosed with both MDD + HIV/AIDS and on AD treatment for > 120 days	127
Total number of patients diagnosed with MDD and on AD treatment for > 120 days. Total number of MDD patients and on AD treatment for > 120 days	12 270
Total number of patients diagnosed with HIV/AIDS	12 397
Number of item dispensed for both MDD and HIV/AIDS	41 086
Number of item dispensed for MDD	466
Article 3.4	
Total number of patients diagnosed with MDD and on AD treatment for > 120 days	22 831
Total number of patients receiving psychotropic agents	4 255
Total number of patient the received both antidepressant (for > 120 days) and psychotropic agents	269 689
Number of item dispensed for MDD	8 142
Number of item dispensed for both MDD and GDs	8 247
Number of item dispensed for GDs	42 896
	529 433

### 1.5.7 Study variables

In this section, the different study variables, both independent and dependent, will be discussed in detail with their definitions as well as a description of each variable.

### 1.5.7.1 Independent variables

Independent variables can be defined as the input or the cause of an illness and can also be referred to as a treatment or an intervention (Starks *et al.*, 2009).

#### 1.5.7.1.1 Age groups

The age of a patient was calculated on the date of treatment received in relation to the date of birth of the patient and using 1 January of the following year as index date for each study year. Therefore, if the date of birth of a patient is 5 May 1980, and treatment was dispensed on 30 August 2010, the patient would be considered to be 30 years of age. Patients were divided into three different treatment groups:

- Age group 1: > 18 and ≤ 40 years
- Age group 2: > 40 and ≤ 60 years
- Age group 3: > 60 years

Only adults were included in the current study. The study population was older than 18 years, because this is when the neurobiological, physiological and mental maturity has been reached (Van De Graaf, 2002).

#### 1.5.7.1.2 Gender

For the purpose of this study, gender was included, and distinguished between male and female patients based on biological differences. Several studies found that females are more prone to develop MDD than males (Cook *et al.*, 2004; McKnight-Eily *et al.*, 2009).

#### 1.5.7.1.3 Treatment period

Treatment period was calculated as the time (in days) from the first prescription for the antidepressants until the last. In article 3.2, the treatment period was divided into three groups as this article looked into initial compliance with antidepressant treatment. We distinguished between the following treatment periods:

- ≤ 30 days
- ≥ 31 and ≤ 120 days
- > 120 days

However, a different treatment period was used in article 3.4, where the study analysed the long-term use of antidepressant treatment and how the treatment period influenced the compliance with antidepressant treatment. In this paper, we distinguished between the following treatment periods:

- 0 to ≤ 120 days
- > 120 to ≥ 365 days
- > 365 days

#### 1.5.7.1.4 Medication

To ensure that the correct type of medication was included, two classification systems were used namely the MIMS classification and NAPPI code. These will be described subsequently:

##### 1.5.7.1.4.1 MIMS (Monthly Index of Medical Specialties) classification

In the MIMS, medication is classed according to their pharmacological mechanism of action (Snyman, 2012). In the current study, the MIMS classification was used as condition to classify the medication and extract medication from the database, e.g. all antidepressants, GABAergic drugs etc.

##### 1.5.7.1.4.2 NAPPI code (National Pharmaceutical Product Interface – Codes for Medication)

NAPPI codes are a nine-digit code assigned to a specific pharmaceutical product and identify a product according to the strength, brand name, pack size and manufacturer (Health Web, 2008; Snyman, 2012). The NAPPI codes of medication were used to extract the required drugs from the database.

#### 1.5.7.2 Dependent variables

The dependent variables can be defined as the output or the effect, while it can also be referred to as the response to an independent variable (Starks *et al.*, 2009).

##### 1.5.7.2.1 Medicine Possession Ratio (MPR)

The MPR is defined as the number of days for which medication is supplied within the refill interval (medicine treatment period) divided by the number of days in the refill interval (Paterson *et al.*, 2000; Steiner *et al.*, 1997; Stein, 2012). The medicine possession rate (MPR) is a well-established method of calculating drug compliance in pharmacoepidemiological studies, including chronic diseases such as MDD (Serna *et al.*, 2010), hypertension (Cramer *et al.*, 2008), osteoporosis (Weycker *et al.*, 2007) and schizophrenia (Weiden *et al.*, 2004). However, it is important to note that the compliance value obtained from the MPR only gives an indication of the possession of medicine by the patient, and that appropriate consumption of medicine is assumed to ensue from possession.

$$\text{MPR} = \frac{\text{Sum the days of supplied medication}}{\text{Number of days in refill interval}} \times 100$$

The MPR is considered acceptable if the calculated value is  $\geq 80\%$ , but  $\leq 110\%$  (Serna *et al.*, 2010). The following criteria were used to measure AD compliance. An MPR of less than 80% indicates the presence of refill gaps with ADs so that possession is considered unacceptably low (undersupply), whereas an MPR greater than 110% is considered unacceptably high (oversupply).

The usage of medicine claims data to determine the MPR calculations is useful in that it is acceptably accurate, convenient, objective, non-invasive and relatively inexpensive to obtain when a large study population is needed (Zhao *et al.*, 2013). It is therefore suitable for the calculation of MPR as an indication of patient compliance with medication therapy (Zhao *et al.*, 2013).

The limitations of using the MPR as a proxy of compliance include the following:

- The MPR can only be calculated if a patient has filled more than two prescriptions.

- Secondly, MPR can only assess whether the medication was collected consistently.
- Lastly, the MPR cannot measure whether a patient was compliant with the instructions given by the medical practitioner (Zhao *et al.*, 2013).

#### 1.5.7.2.2 Compliance and non-compliance

For the purpose of this study, the MPR was used to determine antidepressant compliance in patients diagnosed with MDD. In order to treat MDD effectively and to prevent relapse, patients must be on chronic treatment for at least 120 days or more (NICE, 2009; Keller *et al.*, 2002; Paterson *et al.*, 2000). Conversely, a patient was considered compliant with his/her AD treatment if the MPR was  $\geq 80\%$  and  $\leq 110\%$ , and AD treatment period was longer than 120 days. All AD patients with MPR  $< 80\%$ , meaning they were under supplied or MPR  $> 110\%$ , which means these patients were over supplied and/or an AD treatment period  $< 120$  days, were deemed non-compliant.

A patient on GDs was considered compliant with his/her GD treatment if the MPR was  $\geq 80\%$  and  $\leq 110\%$ . All patients on GDs with MPR  $< 80\%$ , meaning they were under supplied or MPR  $> 110\%$ , which means these patients were over supplied, were deemed non-compliant.

#### 1.5.7.2.3 Prescribed daily dosage

The prescribed daily dosage (PDD) is defined as the mean dose prescribed per day according to a representative sample of prescriptions (WHO, 2003). The PDD is used when a drug has more than one indication, but the dosage for each indication differs. The average daily amount of a drug prescribed was determined through the PDD.

In article 2 the prescribed daily doses (PDDs) were calculated by multiplying the number of tablets (or other dosage forms) dispensed by the tablet strength, divided by the days' supply (treatment period).

In the current study, the initial PDD and the final PDD were compared to each other to determine the effect of non-compliance on PDD. The PDD was used because antidepressants have several off-label indications.

#### 1.5.7.2.4 Prevalence of MDD and HIV/AIDS

Prevalence can be described as the number of patients currently having a specific illness in a given population at a specific time (Waning & Montagne, 2001). In the current study, prevalence was used to describe the existing cases of MDD and HIV/AIDS in the private health sector in South Africa based on the frequency of patients who received AD and ARV medication.

### 1.5.8 Data analysis

All statistical analyses were performed using SAS Version 9.1.3 system (SAS Institute C, NC). All statistical significance was considered with a two-sided probability of  $p < 0.05$ . The practical significance of results was computed when the results were found to be statistically significant ( $p \leq 0.05$ ).

Variables were expressed using descriptive statistics such as frequencies (n), percentages (%), means, medians, standard deviations, and 95% confidence intervals (CI). Inferential statistics were done as indicated for the different articles.

### 1.5.8.1 Statistical analysis according to the different articles

Article	Statistical analyses used
Article 3.2	<p>Chi-square test was used to determine whether an association exists between proportions of two or more groups (age groups vs. MPR groups) (Pagano &amp; Gauvreau, 2000; Adams &amp; Lawrence, 2015). The Cramer's <math>V</math> statistic was used to test the practical significance of the association between proportions of two or more groups (Adams &amp; Lawrence, 2015)</p> <p>The two-sample <math>t</math>-test allowed us to compare the mean MPR of male and female patients (Pagano &amp; Gauvreau, 2000).</p> <p>The one-way ANOVA was used to test differences between three or more means and to calculate differences in the adjusted PDD changes between compliant and non-compliant patients (Brink <i>et al.</i>, 2013). It was operationalised with the general linear model (GLM) procedure of the SAS Version 9.1.3 system. If a difference was indicated, a Tukey multiple comparison test was performed to determine which groups most significantly influence the overall difference between groups (Adams &amp; Lawrence, 2015).</p> <p>Cohen's <math>d</math> was used to evaluate effect size between means (with <math>d \geq 0.8</math> defined as practically significant) (Cohen &amp; Lea, 2004).</p> <p>The correlation coefficient, <math>r</math>, was used to indicate a possible negative association between the initial PDD and change in PDD. (<math>r &lt; -0.5</math>; <math>p = 0.0001</math>). (Adams &amp; Lawrence, 2015).</p>
Article 3.3	<p>The two-sample <math>t</math>-test allowed us to compare the mean MPR of male and female patients as well as the mean MPR and gender (Pagano &amp; Gauvreau, 2000).</p> <p>The one-way ANOVA was used to test differences between the mean MPR of different age groups and antidepressant class (Brink <i>et al.</i>, 2013).</p> <p>It was operationalised with the general linear model (GLM) procedure of the SAS Version 9.1.3. If a difference was indicated, a Tukey's multiple comparison test was performed to determine which groups differ significantly from each other (Adams &amp; Lawrence, 2015).</p> <p>Cohen's <math>d</math> was used to evaluate effect size between means (with <math>d \geq 0.8</math> defined as a large effect with practical significance) (Cohen &amp; Lea, 2004).</p> <p>The Chi-square test (<math>\chi^2</math>) was used to determine whether an association exists between proportions of two or more groups (compliance vs. active ingredients) (Pagano &amp; Gauvreau, 2000; Adams &amp; Lawrence, 2015).</p> <p>The Cramer's <math>V</math> statistic was used to test the practical significance of this association (with Cramer's <math>V \geq 0.5</math> defined as practically significant) (Adams &amp; Lawrence, 2015)</p>
Article 3.4	<p>Chi-square test (<math>\chi^2</math>) was used to determine whether an association exists between proportions of two or more groups (illness vs. MPR groups) (Pagano &amp; Gauvreau, 2000; Adams &amp; Lawrence, 2015).</p> <p>The Cramer's <math>V</math> statistic was used to test the practical significance of this association (with Cramer's <math>V \geq 0.5</math> defined as practically significant) (Adams &amp; Lawrence, 2015)</p> <p>The two-sample <math>t</math>-test allowed us to determine differences in the AD treatment period of AD patients on GABAergic drugs with acceptable vs. unacceptable AD compliance.</p> <p>Cohen's <math>d</math> was used to evaluate effect size between means (with <math>d \geq 0.8</math> defined</p>

as practically significant) (Cohen & Lea, 2004).
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## **1.6 Ethical considerations**

This study was approved by the Research Ethics Committee of the North-West University (NWU-0046-08-A5) and the Board of Directors of the South African Pharmaceutical Benefit Management (PBM) company. Data were analysed anonymously.

## **1.7 Value of the current thesis**

To the best of our knowledge, the current study is the first prospective study of its kind both globally and in South Africa. The study takes an in-depth look at the current situation in the private healthcare sector of South Africa regarding non-compliance with antidepressant treatment and possible causes for non-compliance. This study is also the first in South Africa to make use of a medical claims database and apply pharmacological dogmas in order to deliver meaningful clinical assumptions regarding the data at hand. Furthermore, in the current economy, the procurement of funding for research projects such as the current study is a bleak endeavour. Therefore, the research methodology established in the current study is relatively inexpensive and can be used to make an impact when resources are limited.

## **1.8 Chapter summary and outline of the study**

In summary, Chapter 1 provides the reader with the necessary background to understand the aims, objectives and methodology that will be used and achieved in this study. This chapter also serves as a methodology section in which the methods to be used in this study were explained in detail.

Chapter 2 is a literature study describing the aetiology, epidemiology, latest treatment trends, classes of antidepressants and illnesses closely associated with MDD.

Chapter 3 consists of the four research articles regarding the findings of the current study. The first article was written in order to determine the consequences of non-compliance with antidepressant treatment and to establish that non-compliance is a well-recognised yet poorly understood phenomenon. The manuscript reviews the clinical presentation of the ADS, its possible neurobiology and clinical correlates, and provides a series of new ideas as to the probable underlying neurobiology of the syndrome, and its subsequent impact on the long-term outcome of MDD. Finally, by counterbalancing the review with a new generation antidepressant that does not cause ADS after discontinuation, namely agomelatine, the review provides new insights into the biology and pharmacology of ADS, and takes a serious look at the role of serotonin in antidepressant action. This paper has now been published.

The second article was written as the basis for the methodology used in this thesis. It has established the MPR as a reliable method to report treatment compliance and has determined the prevalence MDD in the current cohort. Furthermore, this study analysed the influence of change in PDD on AD treatment compliance, and has been accepted for publication.

In the third article, the authors investigated the influence of HIV/AIDS (one of the illnesses with the highest prevalence in South Africa) on the compliance with antidepressant medication, looking specifically at the class of AD associated with the best compliance in this population and the association between gender and AD treatment compliance. This paper was submitted and currently still under review.

In the final research article, the authors looked into the association between GABAergic drug co-prescribing with AD treatment and the effect of this co-prescribing of GABAergic drugs on the compliance of AD treatment in the private healthcare sector of South Africa. It also investigated the influence of the treatment period on the treatment compliance as well as looking into the number and class of co-prescribed GABAergic drugs along with AD treatment. This article is included in the current research thesis as a concept article.

These four manuscripts are presented either in their final published form (as a pdf), or in MSWord format (in the case of articles still in review). All are presented in the house style for that particular journal, and as outlined in the instructions to authors (see Addenda 1 to 4).

## CHAPTER 2: LITERATURE STUDY

### 2.1 Introduction

Chapter 2 will focus on the current literature on depression and the different aspects thereof. The cause of depression is a complex interaction between genetic predisposition, social and psychological stressors, and biological factors that can lead to more stress and dysfunction if not diagnosed and treated properly. In this section, I will strive to shed more light on the prevalence, causes and contributing factors of major depression, and also discuss possible neurobiological mechanisms as well as current treatments.

### 2.2 Epidemiology of major depression disorder (MDD)

#### 2.2.1 Prevalence of MDD

MDD is a common disorder affecting an estimated 450 million people worldwide and is at present the primary cause of disability in terms of total years lost due to disability, for both males and females (WHO, 2012). In a World Mental Health Survey reporting on 17 countries, one in 20 people had an episode of depression during the past year (WHO, 2012). In the United States, and elsewhere, women are approximately twice as likely as men to be diagnosed and treated for MDD, while there appears to be no difference between gender in terms of the intensity of symptoms (Bennett *et al.*, 2005). In young children, boys and girls are equally affected, although girls tend to experience higher rates of major depressive episodes (MDEs) at the start of adolescence (Bernal *et al.*, 2007)

A major depressive episode (MDE) causes a great deal of suffering and reduces the affected person's ability to function effectively (WHO, 2012). Depending on the severity and the number of symptoms presented during an episode, depression can be categorised as mild, moderate or severe. During a mild depressive episode, a patient will have some difficulty in performing everyday work and social activities, but will not cease to function completely. An individual with a severe episode will not be able to continue with social or work-related activities and in some cases only function to a very limited extent.

MDD can become a chronic and recurrent illness and without proper treatment can lead to suicide. Every year, approximately 1 million people commit suicide, which translates roughly to 3 000 deaths daily. Furthermore, for every successful suicide there are approximately 20 or more failed attempts (WHO, 2012). The lifetime death by suicide in MDD is frequently cited as 15% (Kiyohara & Yoshimasu, 2009). Although MDD can be treated effectively, less than half of these patients receive the necessary treatment (Demyttenaere *et al.*, 2004; Kohn *et al.*, 2004). In some countries, less than 10% of the affected population receives the proper treatment (WHO, 2010). Effective treatment is limited by the stigma associated with mental illness, shortage of resources, lack of trained healthcare providers and inaccurate assessments (Becker & Kleinman, 2013). Patients with MDD are not always diagnosed correctly, whereas the disorder is also misdiagnosed in patients who do not have MDD. The prescribing of antidepressants (AD) is still a major problem even in high-income countries (Becker & Kleinman, 2013). The prescribing of AD is affected by non-compliance to treatment (Hansen & Kessing, 2007), and treatment failure to first- and second-line treatment regimens (McCombs *et al.*, 1990), which all lead to a significant increase in the cost of treatment due to augmentation strategies and hospitalisation of patients (Schultz & Joish, 2009).

MDD is a mental illness where patients present with decreased energy, disturbed sleep patterns, poor concentration, depressed mood, and loss of interest or pleasure (WHO, 2012). These patients all experience different kinds of symptoms, and different levels of severity, frequency and duration. The disorder can be divided into several different subtypes (NICE, 2009):

- Major depressive disorder (MDD) is associated with a distinct change in mood, characterised by sadness or irritability and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire, constipation, loss of the ability to experience pleasure in work or with friends, crying, suicidal thoughts, and slowing of speech and action. These changes must last a minimum of two weeks and interfere considerably with work and family relationships.
- Dysthymic disorder is characterised by long-term symptoms, usually two years or longer, the symptoms of which are not so severe as to cause disability by influencing a patient's normal functioning and wellbeing.
- Minor depression is where a patient has symptoms for two weeks or longer, but does not meet the full criteria for MDD. If a patient is suffering from minor depression and remains untreated, they have an increased risk of developing MDD.
- Psychotic depression occurs when a patient is suffering from severe depression with psychosis and hallucinations.
- Postpartum depression is experienced by 8 to 25% of women after giving birth, when hormonal and physical changes as well as new responsibilities can be overwhelming (O'Hara & Swain, 1996).
- Seasonal affective disorder is closely linked with the development of depressive symptoms at the start of winter months. The depressive symptoms usually lift during the start of spring and summer.

For the purpose of this study, the focus will be on MDD. Whenever the abbreviation 'MDD' is used in the text, it will refer specifically to 'major depressive disorder', unless noted otherwise.

The DSM-IV TR has basic guidelines for the diagnosis of MDD in the primary healthcare sector. The criteria for MDD (DSM-IV, 2000) are:

- Depressed mood
- Marked reduced interest in almost all forms of pleasure and activities
- Significant loss or gain in weight (>5% body weight)
- Hypersomnia or insomnia
- Psychomotor agitation or retardation
- Fatigue and loss of energy
- Feeling of worthlessness and inappropriate guilt
- Diminished concentration

- Recurrent thoughts of suicide and death

To diagnose the patient with MDD, at least five of the above-mentioned symptoms must have been present in the last two weeks and one of the symptoms must be depressed mood or a loss of interest in activities and pleasure (American Psychiatric Association, 2000).

### 2.2.2 Onset of MDD

MDD normally starts in the late 20s, but affects patients of every age, from young children to elderly people (Goetzel *et al.*, 2003; Grant *et al.*, 2004; Murray & Lopez, 1997). The risk for MDD is relatively low in very young children until their early teens, after which there is a significant increase in risk (Kessler, 2003). In the understanding of the initial development of MDD, it is of utmost importance to focus on the adolescent, particularly since first episodes of MDD may commence during adolescence and recur in later stages of life (Monroe *et al.*, 1999).

Although there is no known trigger for the development of MDD, it is believed to be the result of a combination of environmental and genetic interactions (Weinstock, 2010). MDD may be triggered in vulnerable individuals by a major stressful life event or exposure to chronic stress (Kendler & Karkowski-Shuman, 1997). Stress can be defined as a constellation of events, which begins with a stressor that precipitates a reaction in the brain, which subsequently activates a cascade of physiologic systems in the body (Dhabhar & McEwen, 1997; Dhabhar & McEwen, 1999). The ability to adapt under stress varies considerably between individuals and, in those who do not suitably adapt to the stressor, adversity may lead to impaired regulation of the hypothalamus pituitary adrenal (HPA) axis, continuous cortisol release (hypercortisolemia) with neuronal shrinkage and associated changes in serotonergic and noradrenergic neurotransmission (Weinstock, 2010). The vulnerability to develop MDD during stressful life events is greater in patients with a family history of MDD and in people exposed to physical and sexual abuse during childhood (Bifulco *et al.*, 1991; Phillips *et al.*, 2005). Several studies have also established the importance of prenatal stress as a risk for the child developing MDD in later life, such as the mother suffering from MDD during pregnancy (Field & Diego, 2008; Watson *et al.*, 1999), or infection (Machon *et al.*, 1997) or alcohol abuse (O'Connor & Kasari, 2000) during pregnancy. Postnatal stressors such as child maltreatment (Margolin & Gordis, 2000), physical and sexual abuse (Sedlack & Broadhurst, 1996), the stress associated with the loss of a parent (Agid *et al.*, 2000) and growing up with a parent suffering from a mental disorder who then provides insufficient care (Hedin & Janson, 2000) have been associated with an increased risk of suffering from MDD and other mood disorders later in life.

During the physiologic stress response, neurotransmitters and hormones are released that serve as the brain's messengers to the body in order to respond appropriately and to adapt to a stressor (Kiyohara & Yoshimasu, 2009). Over a short period of stress, the physiologic response is adaptive and is an essential survival mechanism for an animal or person (termed allostasis; see (Harvey *et al.*, 2003). However, severe physiological damage can be induced if the applied stressor is excessive or if the normal physiological response mechanism that curbs the stress response is either not activated or becomes maladaptive (Dhabhar & McEwen, 1997; McEwen & Seeman, 1999). This is termed allostatic load. In humans and animals, the cortisol/corticosterone rhythm is an important marker of the damaging effects of chronic stress (Dhabhar & McEwen, 1997; Sephton *et al.*, 2000). The chronic release of glucocorticoid stress hormones is widely regarded as immunosuppressive (Munck *et al.*, 1984), whereas prolonged glucocorticoid release bolsters glutamate release, which is a potent neuro-excitant and toxin in the brain. If left unchecked, glutamate is ultimately responsible for structural brain changes (see below), as is evident in neuroimaging studies in depressed patients (e.g. hippocampal volume loss (Harvey *et al.*,

2003)). The latter brain region is critical for the regulation of the stress response as well as maintaining memory and other cognitive processes (Harvey *et al.*, 2003). Therefore, a dysregulated stress response and long-term glucocorticoid exposure can be extremely harmful to health (Kiyohara & Yoshimasu, 2009; Munck *et al.*, 1984).

The risk for MDD is increased by on-going adverse conditions and events such as illness, medical disability, divorce, loss of a loved one, poverty, unemployment and a lack of social support (Bruce & Hoff, 1994; Kiyohara & Yoshimasu, 2009; Simon, 2003). The clinical consequences of stress lead to the disabling of the circadian clock, the hypothalamic-pituitary-adrenal (HPA) axis, and the disruption of inhibitory-excitatory  $\gamma$ -amino butyric acid (GABA)-glutamate signalling with insufficient neurotrophin release, such as brain-derived neurotrophic factor, culminating in structural changes in critical brain regions regulating the stress response, for example the hippocampus (see Harvey *et al.*, 2003; Krishnan & Nestler, 2008; Savitz & Drevets, 2009; Renoir *et al.*, 2012). These diverse and interlinked cascades end up in disorganised biorhythms and diminished brain monoamines (5-HT, NA and DA), and these deficits in monoamine are thought to play a key role in the behavioural and cognitive symptomology of depression.

ADS is more frequently observed in patients following chronic AD treatment and is also closely associated with higher dosages (Hosenbocus & Chahal, 2011), suggesting that, like in the case of AD initiation (see Manji *et al.*, 2001; Popoli *et al.*, 2002; Krishnan and Nestler, 2008, for review), repeated non-compliance and ADS induce a variety of time-dependent neuroplastic changes. Indeed, the discontinuation of paroxetine during the maintenance phase of treatment for depression demonstrates a neuroendocrine stress response (Michelson *et al.*, 2000), while antidepressant discontinuation is associated with distinct functional changes in the brain (e.g. Henry *et al.*, 2003; Kaufman *et al.*, 2003). That ADS increases a bio-behavioural stress response suggests that prolonged damaging may result in a compromised outcome, especially by introducing an additional risk factor into an already vulnerable individual, with the associated risk of relapse and recurrence (Harvey *et al.*, 2003)

Theories based on altered biogenic amines have long been the most supported hypotheses that describe the biology of MDD, and these include the biogenic amine hypothesis and the adrenergic-cholinergic balance hypothesis (Harvey, 1997; Pittenger & Duman, 2008; Chau *et al.*, 2001). Although in some ways obsolete, these hypotheses are still nevertheless important since all currently used ADs target neurobiological targets suggested by these hypotheses, viz. NA, 5-HT, DA, MAO and both NA and 5-HT transporters. However, recent studies have begun to suggest that MDD has a much more complex aetiology involving altered neuroendocrine, neurotoxic/protective, neuroplasticity and neuroinflammatory processes (Harvey, 2008; Sarandol *et al.*, 2007).

The exact cause of MDD remains unknown and there is much on-going research aimed at identifying the illusive neurobiological target/s responsible for the illness, as well as searching and designing new generation ADs with improved efficacy in treating the illness. The most prominent modern theories and hypotheses will now be discussed.

### **2.2.2.1 The monoamine hypothesis of MDD**

In the early 1950s isoniazid and iproniazid were developed for the treatment of tuberculosis, when the researchers noticed that these drugs possess mood elevating effects in individuals suffering from both depression and tuberculosis (Selikoff & Robitzek, 1952; Salzer & Lurie, 1953). On further investigation, it was found that iproniazid has monoamine oxidase (MAO) inhibiting properties (Griesemer *et al.*, 1953).

Around the same time, Freis noticed that several hypertension patients treated with reserpine (which depletes monoamine stores) develop depressive-like symptoms (Freis, 1954). These observations can be considered as the start of modern AD drug development. Furthermore, these discoveries, among others, led to the classical monoamine hypothesis of depression (Schildkraut, 1965). The monoamine hypothesis of depression states that depression is caused by a deficiency in monoaminergic activity in the brain and drugs that increase monoaminergic neurotransmission can alleviate depressive symptoms (Schildkraut, 1965).

After the discovery of the antidepressant, imipramine, a tricyclic compound with a similar structure to that of chlorpromazine (Kuhn, 1958), several other tricyclic antidepressants were developed that are still in use today. The first drug that yielded an antidepressant effect without inhibiting the reuptake of monoamines was mianserine, an atypical AD (Leonard, 1978). Mianserine acts as an AD by blocking presynaptic  $\alpha_2$ -adrenergic autoreceptors, which leads to an increase in noradrenergic neurotransmission. In the late 1980s and early 1990s, we saw the introduction of the selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and fluoxetine (Fuller, 1995). During this period, another atypical AD was discovered, namely mirtazapine that antagonises  $\alpha_2$ -autoreceptors as well as serotonergic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors (Smith *et al.*, 1990). All the above-mentioned AD agents modulate the monoamine neurotransmission and therefore support the monoamine hypothesis of depression.

The monoamine hypothesis of depression has a number of limitations, as it fails to explain several observations.

- Firstly, changes occur in the synaptic monoamine concentrations directly after the administration of an AD, but the therapeutic response is only achieved after several weeks (Baldessarini, 1989).
- Secondly, several other drugs, such as cocaine and amphetamine, also increase brain monoaminergic activity, but are not clinically active antidepressants (Fischman & Foltin, 1991).

In the last decade, the thinking regarding pathophysiology and AD action suggests that drugs that initially increase monoamine levels ultimately activate secondary effects on cellular and molecular plasticity (Nestler *et al.*, 2002; Ansorge *et al.*, 2007). Cellular and molecular changes ultimately lead to the restoration of synaptic connectivity that is needed for neurotransmission in order to alleviate depression (Manji, 2003). Moreover, these changes only occur after chronic treatment and it seems to rely on alterations in gene expression. For instance, it has been proposed that the upregulation of the transcription factor, CREB, caused by the chronic treatment with SSRIs directly correlates with the onset of antidepressant-like effects in animal models (Pittenger & Duman, 2008).

In summary, the observations mentioned above prompted a revision of the biochemical basis of depression and it was concluded that the monoamine hypothesis of depression alone cannot fully explain the clinical syndrome of depression. Therefore, a more comprehensive hypothesis is needed to explain and incorporate current findings.

### **2.2.2.2 Cholinergic hypothesis of depression**

The cholinergic hypothesis is based on the cholinergic-adrenergic imbalance theory that was described in the early 1970s (Janowsky *et al.*, 1972). The cholinergic-adrenergic imbalance theory suggested that an over-activity of cholinergic neurotransmission over adrenergic neurotransmission causes depression, while mania is caused by the opposite of this imbalance (Janowsky *et al.*, 1972). In the 1990s, it was

suggested that depressed patients exhibit a cholinergic sensitivity, which could be seen as an exaggerated behavioural or hormonal response in cholinergic agonists (Janowsky et al., 1994). Moreover, some authors have suggested that muscarinic receptors in the nucleus accumbens may play a role in depression and AD action (Chau et al., 2001) and a study by Furey and Drevets found that scopolamine (an anticholinergic agent) can be used as an augmentation strategy with ADs for the treatment of treatment resistant depression (TRD) (Furey & Drevets, 2006). In the end, the cholinergic hypothesis was never a popular theory, perhaps because anticholinergic drugs never materialised as effective ADs.

### **2.2.2.3 HPA axis hyperactivity hypothesis**

Hypothalamic-pituitary-adrenal axis (HPA axis) hyperactivity and the defective HPA axis glucocorticoid feedback mechanism are closely associated with MDD (Pace et al., 2007; Kupfer et al., 2012). MDD patients have shown increased concentrations of cortisol in cerebrospinal fluid, plasma and urine (Pariante & Miller, 2001). The HPA axis hyperactivity seen in MDD patients might be due to the hyper-secretion of the corticotrophin-releasing factor (CFR) (Pariante & Miller, 2001). The administration of CFR has demonstrated behavioural changes in animals that correlate with what is seen in humans with MDD. These behavioural changes include, inter alia, the following: modified sleep, appetite, cognition, mood and locomotor activity. Therefore, the hyper-secretion of CFR may contribute to the behavioural changes displayed in MDD patients (Nemeroff, 1996). The increased CFR levels in MDD patients is believed to be related to the failure of the negative feedback regulation of cortisol to suppress the hyper secretion of CFR and is suggested to be caused by glucocorticoid resistance involving glucocorticoid receptors (GR) (Plotsky et al., 1998; Pariante, 2004; Walker et al., 2010). Disturbances in the HPA axis have a direct negative effect on the circadian rhythms, as seen in MDD patients, and this finding paved the way for the development of the latest AD, namely agomelatine that targets the bio-rhythms in the suprachiasmatic nucleus of the hypothalamus (Monteleone & Maj, 2008; de Bodinat et al., 2010). Increased levels of cortisol over prolonged periods of time may damage hippocampal neurons, a brain region closely associated with MDD (McEwen, 2000; Sapolsky, 2000). Several studies have found a reduction in the volume of the hippocampus in depression subjects (Sheline, 2003; Duman, 2004). See section 2.1.3.1 for more detail regarding the reduction in hippocampus volume.

### **2.2.2.4 Immunological hypothesis of depression**

MDD is closely associated with the activation of the immune system. Several cytokines that are closely associated with inflammation (e.g. IL-1, IL-2, IL-6 and TNF- $\alpha$ ) were found to be increased in the plasma and cerebrospinal fluid of MDD patients and can be reversed with AD treatment (Raison *et al.*, 2006). Increased levels of cytokines were found to cause sickness in both animals and humans with symptoms very similar to that of MDD, such as cognitive function, altered mood and neurovegetative functioning (Dantzer, 2004). A further linkage between inflammation and depression is the fact that patients treated with INF- $\alpha$  for cancer and viral infections such as Hepatitis often met the criteria of MDD (Renault & Hoofnagle, 1989; Muraoka *et al.*, 1996; Sotelo *et al.*; 2014). It is believed that cytokines cause depression effecting both neurotransmitter function and synaptic plasticity (Raison *et al.*, 2006). Furthermore, the effects of cytokines on the endocrine system during MDD is well documented, and may be related in part to their effects on the glucocorticoid receptors signalling pathways and may play a role in glucocorticoid resistance (Pace *et al.*, 2007). Therefore, it seems like there is a strong interlink between the immune system and the endocrine system in the neuropathophysiology of MDD.

### **2.2.2.5 Neuroplasticity hypothesis**

The volumetric decrease in the hippocampus and certain forebrain regions was observed in individuals with chronic MDD (Sheline, 2003; Duman, 2004). These observations laid the foundation for the development of the neuroplasticity hypothesis that implicates decreases in neurotrophic factors that regulate plasticity within the adult brain (Manji *et al.*, 2003; Duman & Monteggia, 2006) and also accounts for changes in the monoaminergic neurotransmission by suggesting that drugs that increase monoamine levels acutely will ultimately activate secondary effects on molecular and cellular plasticity (Nestler *et al.*, 2002; Ansorge *et al.*, 2007). Depression is relieved when the above-mentioned changes may facilitate the restoration of synaptic connectivity needed for normal neurotransmission (Manji *et al.*, 2003). Additionally, several authors have implicated the glutamate/NO/cGMP/PK-G pathway to play a key role in neuroplasticity (Zarate *et al.*, 2003; Calabrese *et al.*, 2007; Kleppisch & Feil, 2009) and drugs that modulate this pathway seemed to alleviate depressive symptoms (Zarate *et al.*, 2002; Zarate *et al.*, 2003).

In summary, there is a wide range of postulations for the development of MDD, but all of the above-mentioned hypotheses have in some or other way the inability to describe certain phenomena associated with MDD. Therefore, more research is needed into the neuropathophysiology and the development of MDD to bring forward a more unifying theory that can elucidate all the different facets of this debilitating illness.

### **2.2.3 The neurobiology of MDD**

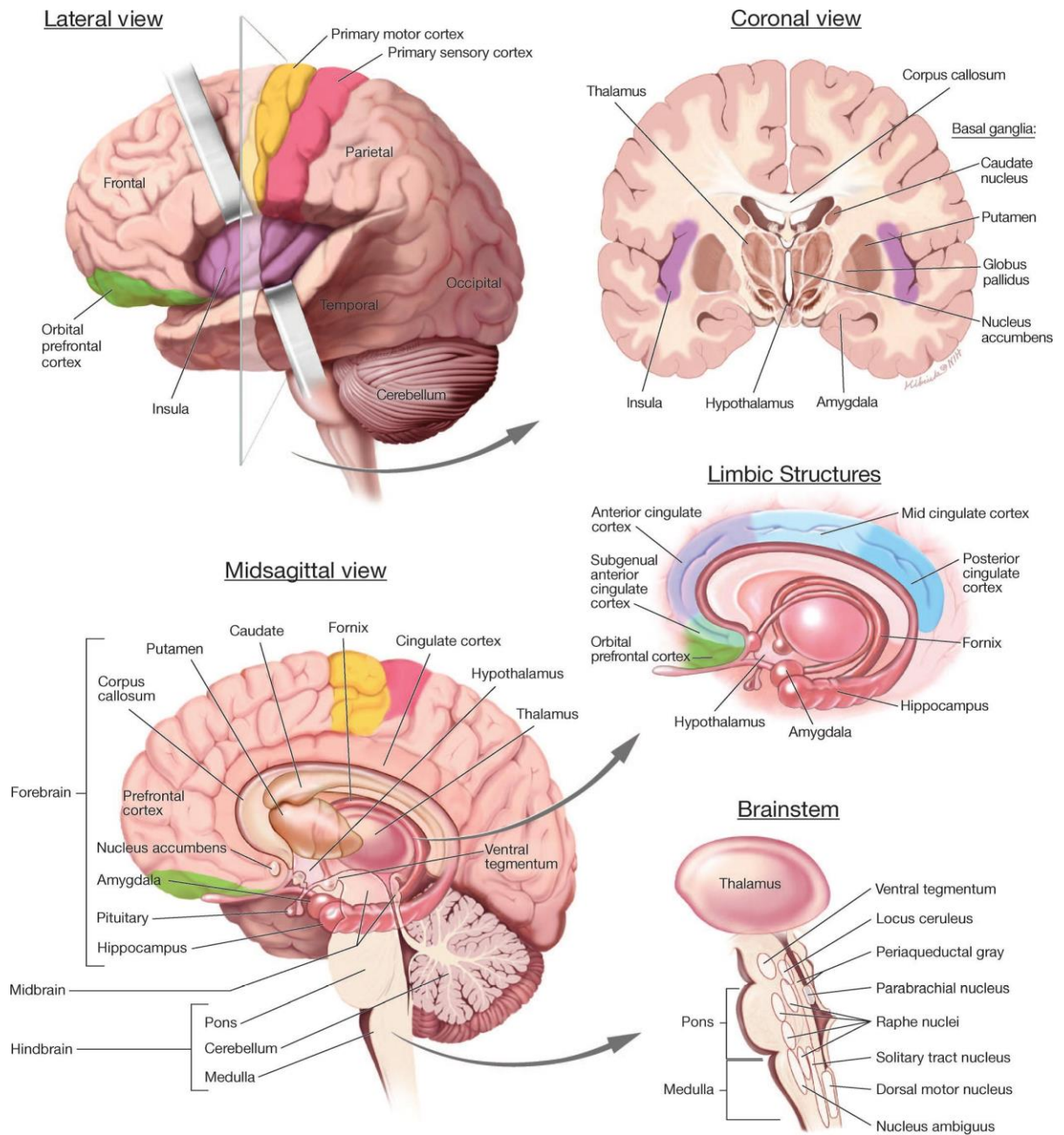
#### **2.2.3.1 The functional and structural brain changes associated with MDD.**

In the last decade, substantial progress has been made in neuroimaging methods, although there is much to learn in order to better understand the underlying pathophysiology and the structural and functional changes associated with MDD.

Neuroimaging has revealed some neurobiological abnormalities associated with MDD, with a specific focus on prefrontal and limbic structures and interconnected circuits that play an important part in effective regulation (Maletic *et al.*, 2007). These pathways include the ventromedial prefrontal cortex (VMPFC), lateral orbital prefrontal cortex (LOPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), ventral striatum, nucleus accumbens, amygdala and the hippocampus (depicted in Figure 2.1) (Davidson, 2003; Drevets, 1998). Patients with MDD display abnormalities in these brain areas when compared to healthy controls, suggesting a biological basis for the illness and its symptoms (Davidson, 2003; Drevets, 1998; Savitz & Drevets, 2009).

The prefrontal cortex, cingulate, amygdala and the hippocampus not only play a role in mood regulation, but are also critical in learning and contextual memory processes (Phelps *et al.*, 2004). The VMPFC, on the other hand, mediates pain, sexual functioning, aggression and eating behaviours, whereas the LOPFC assesses risk and controls poorly adaptive and protective behaviours (Blair, 2001; Blair & Cipolotti, 2000). These two brain areas have a dual pattern of activity with the DLPFC, which supports executive function, attention and working memory processes (Kane & Engle, 2002; Maletic *et al.*, 2007). The dorsal part of the ACC plays a part in the cognitive and motor functioning network (Bush *et al.*, 2000), whereas the ventral ACC is involved in assessing emotional and motivational networks (Devinsky *et al.*, 1995; Vogt *et al.*, 1992). The ACC is also involved in outcomes of behaviour and cognition and to enable adjustments based on changing eventualities (Bush *et al.*, 2000; McCormick *et al.*, 2006).





**Figure 2.1:** Anatomy of the human brain in three different views; lateral, coronal and midsagittal. The function of this illustration is to indicate the different parts of the brain affected by MDD as discussed in the text and also serves as a guide to the reader to show where the different brain structures associated with MDD are positioned in the brain (Lane et al., 2009).

In a regional blood flow study in patients with depression, Drevets reported hyperactivity in the VMPFC and LOPFC as well as hypoactivity in the DLPFC (Drevets, 1998). From a functional point of view, this abnormal activity in the VMPFC, LOPFC and the DLPFC may be responsible for the symptoms of MDD (Maletic *et al.*, 2007). The hyperactivity in the VMPFC is closely associated with the heightened sensitivity to symptoms such as pain, anxiety, tension and depressive thoughts, whereas hypoactivity in

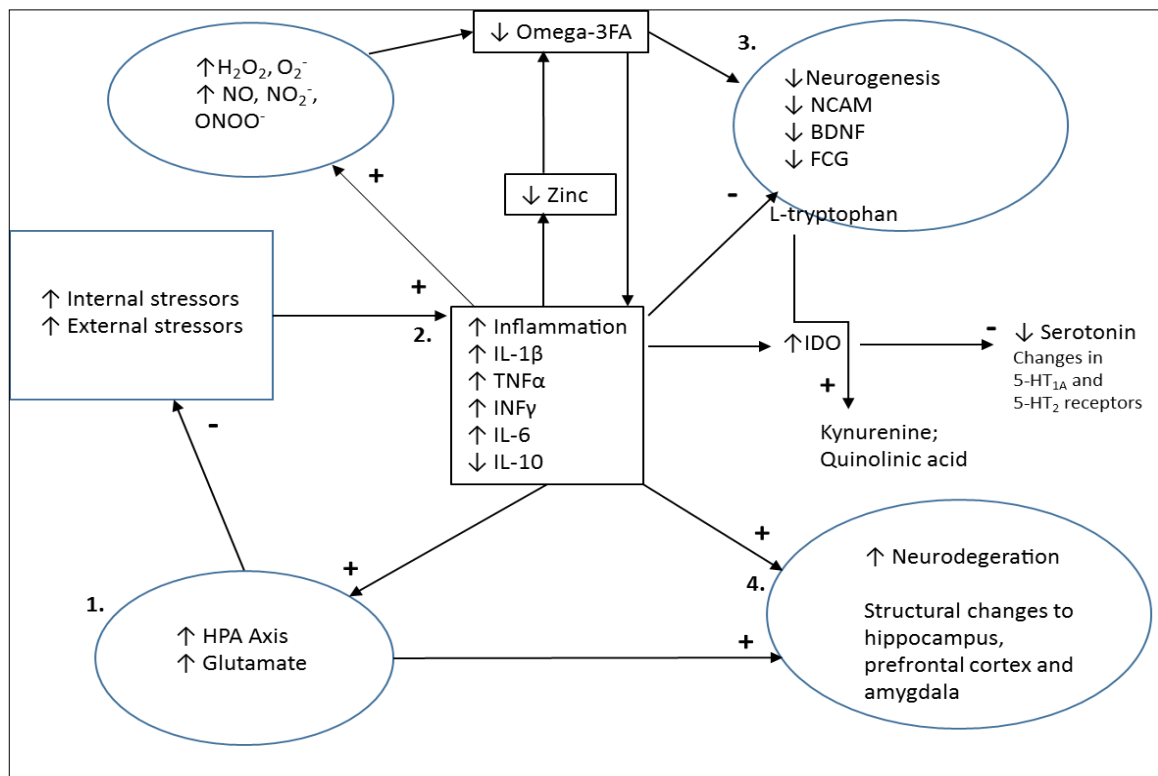
the DLPFC may cause deficits in working memory and attention, apathy and psychomotor retardation (Drevets, 1998; Maletic *et al.*, 2007). In a study by Anand and co-workers, who applied functional Magnetic Resonance Imaging (fMRI) in connectivity studies, it was suggested that a possible decrease in communication between the ACC and the amygdala may be at play in MDD (Anand *et al.*, 2005). The result of this decrease in communication can be caused by a failure of the ACC to serve its inhibitory role in emotion regulation (Whittle *et al.*, 2006) resulting in more motivational and affective disruption (MacDonald *et al.*, 2000; Maletic *et al.*, 2007).

The hippocampus is another structure implicated in MDD (Nestler *et al.*, 2002). Several studies have found a significant decrease in the volume of the hippocampus in MDD patients when compared to healthy individuals (Neumeister *et al.*, 2005; Sheline *et al.*, 2003; Videbech & Ravnkilde, 2004). The decrease in hippocampal volume is bilateral, although both hippocampus hemispheres, left and right hippocampus, show a slightly larger decrease in total volume (Videbech & Ravnkilde, 2004:1964; Macqueen *et al.*, 2003:1392). Moreover, a direct relation has been found between the number and duration of untreated depressive episodes and hippocampal volume reduction evident in MDD (Sheline *et al.*, 2003). In patients with recurrent MDD, their hippocampal volume has been found to be significantly smaller even after remission of an episode when compared to healthy individuals (Neumeister *et al.*, 2005). Of relevance to this study, Macqueen and colleagues (2003) described an association between antidepressant switching and greater hippocampal volume changes in MDD (Macqueen *et al.*, 2003:1391).

### **2.2.3.2 Molecular changes in MDD**

The molecular processes involved in the pathophysiology of MDD can be divided into at least three main categories of peripheral hormone type factors (Kupfer *et al.*, 2012), and are depicted in Figure 2.2.

- Impaired regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis.
- Proinflammatory cytokines, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6) and tumour-necrosis-factor- $\alpha$  (TNF $\alpha$ ).
- Neurotrophic factors and other growth factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor and insulin-like growth factor-1.



**Figure 2.2: Inflammatory and neurodegenerative pathways in depression. The molecular changes associated with MDD. (1) Indicates the impaired regulation of the HPA axis, (2) the proinflammatory cytokines that play a role in the weakening of neurotrophic support and monoamine neurotransmission, (3) the decrease in neurotrophic factors such as BDNF that leads to a decrease in neurogenesis and (4) the structural changes seen in the hippocampus, PFC and the amygdala due to neurodegeneration. This figure was adapted from (Harvey, 2008; Maes et al., 2009).**

The changes in the hippocampus, as mentioned above, increase the potential for neuroendocrine dysregulation via irregular feedback of the HPA axis (Kupfer *et al.*, 2012; Maletic *et al.*, 2007) (see (1) in figure 2-2). High levels of cortisol are a constant finding in MDD patients and may play a role in impaired neuroplasticity and cellular resilience (Manji *et al.*, 2003). The susceptibility of the hippocampus to neuronal damage may be increased by the imbalance between glucocorticoid and mineralocorticoid receptors in MDD along with high density glucocorticoid receptors (GR) (de Kloet *et al.*, 2007). Therefore, the consequent hippocampal atrophy could result in further neuroendocrine dysfunction and therefore increases the risk of maladaptive bio-behavioural changes typical of MDD (Nestler *et al.*, 2002). Post-mortem comparisons of brain tissue in patients with MDD and age-matched healthy individuals have shown a decrease in the total volume of the hippocampus (Neumeister *et al.*, 2005). The shrinkage was caused by an increased density in neuronal cells and a significant reduction in dendritic branching and spine complexities (Stockmeier *et al.*, 2004).

The outcome of increased glucocorticoids and compromised hippocampal functioning might also include a down-regulation of GR sensitivity. Under chronic stress, the decrease in GR sensitivity can have a negative outcome as GR sensitivity becomes insufficient to stop the initial stress response as part of the natural negative feedback process (Raison, 2003; Raison *et al.*, 2006). The resulting over activity of the

HPA axis, in combination with the amygdala activation, leads to an increase in sympathetic tone and an increased release of cytokines from macrophages (Konsman *et al.*, 2002). The increase in pro-inflammatory cytokines has been linked to the decrease in GR sensitivity and a loss of insulin sensitivity, which further increases the probability of metabolic and neuroendocrine abnormalities (Wieseler-Frank *et al.*, 2005) (see (2) in Figure 2.2). The symptomology associated with the disruption caused by pro-inflammatory cytokines includes typical sickness behaviour, such as loss of libido and appetite, fatigue and hypersensitivity to pain (Tsigos & Chrousos, 2002).

Pro-inflammatory cytokines may also weaken neurotrophic support and monoamine neurotransmission that can lead to neuronal apoptosis and glial damage (Mossner *et al.*, 2007). Changes in the glial-neuron relationships have been highlighted in the aetiology of MDD and neuropathic pain (Rajkowska & Miguel-Hidalgo, 2007; Wieseler-Frank *et al.*, 2005). Glia cells play an intricate role via their interaction with neurons in which astroglia and microglia maintain the homeostasis of the neuronal environment by modulating electrolytes, neurotransmitters and neurotrophic factors (Bessis *et al.*, 2007). Neurons interchange support of glial functions via neurotrophin signalling. Furthermore, peripheral immune dysregulation, depression and stress lead to the activation of microglia that then contribute to the existing immune disruption by means of the further release of inflammatory cytokines (Frank *et al.*, 2007).

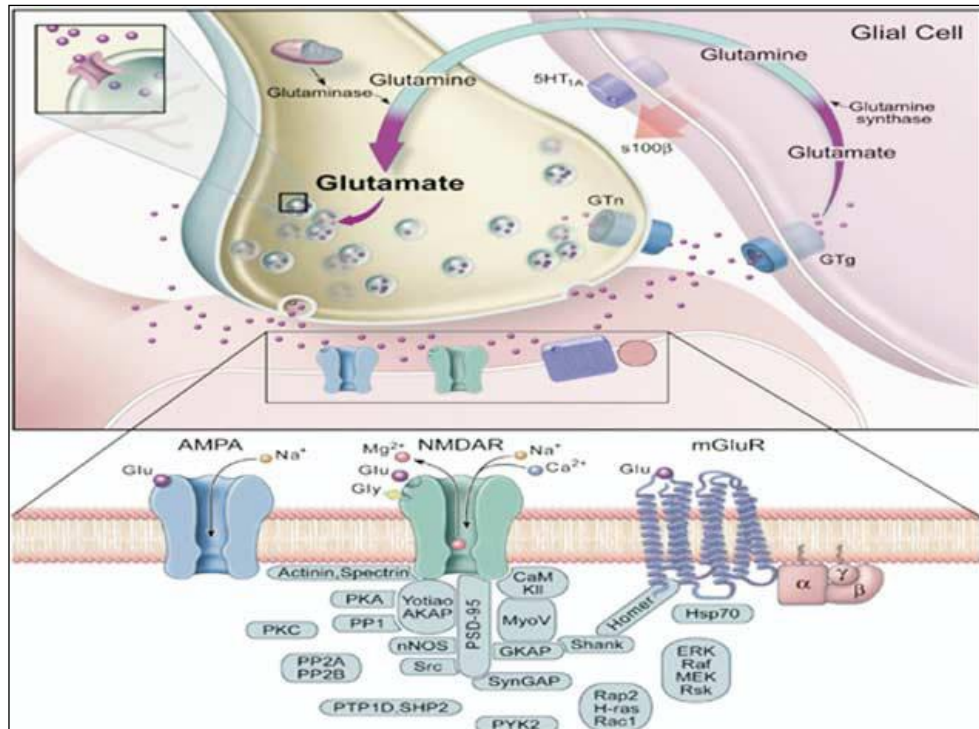
Brain-derived neurotrophic factor (BDNF) plays an integral part in mediating the health of glial-neuron interactions (Duman *et al.*, 1997). BDNF is involved in neurogenesis and is the primary neurotrophin in the hippocampus (Manji *et al.*, 2003). This neurotrophin is a dimeric protein widely spread throughout the brain, is structurally related to nerve growth factor and is involved in vital cellular processes such as neuroplasticity, cell maintenance and apoptosis (Tapia-Arancibia *et al.*, 2004). In order to promote cellular resilience and long-term potentiation, BDNF interacts with its receptor, tyrosine receptor kinase receptor (TRkB). However, the precursor form of BDNF, viz. pro-BDNF, causes a reduction in dendritic spines and promotes apoptosis in the peripheral nervous system by binding to the p75<sup>NTR</sup> receptor. As such, p75<sup>NTR</sup> is a member of the tumour necrosis factor family and has an opposite effect to that of TRK receptors (Beattie *et al.*, 2002; Dechant & Barde, 2002; Lee *et al.*, 2001; Maletic *et al.*, 2007). Depending on its expression, BDNF can condense neural networks in an activity-dependent manner that is regulated by a number of neurotransmitters, such as acetylcholine (ACh), dopamine (DA), glutamate, GABA, norepinephrine (NE), serotonin (5-HT) (Lu *et al.*, 2005).

Several preclinical and clinical studies suggest a dysregulation of BDNF in conditions of chronic stress and depression (Duric & McCarson, 2005; Karege *et al.*, 2005; Shimizu *et al.*, 2003). Acute and chronic immobilisation stress in animal models results in a decrease of BDNF expression, with the same result observed in acute and chronic pain models (Duric & McCarson, 2005). Overall, the majority of studies have found significantly lower levels of serum BDNF in untreated MDD patients compared to treated and healthy patients (Shimizu *et al.*, 2003); however, recent papers (e.g. Harvey *et al.*, 2013) and meta-analyses (e.g. Molendijk *et al.*, 2013) have now revealed that this observation is by no means definitive. Since BDNF exerts global effects on neuroplasticity that may in the end be beneficial or detrimental, Harvey and colleagues (2013) have described evidence that BDNF counter regulates changes in redox and metabolic status in MDD so that it may mediate undesirable redox and metabolic changes associated with MDD. Interestingly, a significant reduction in both BDNF and neurotrophin (NT-3) has been described in post-mortem analyses of brains from patients who committed suicide, compared to a non-suicide control group (Karege *et al.*, 2005).

From the above findings, the neurotrophic hypothesis has developed into a key theory to explain the molecular pathogenesis of MDD. In this theory, stress and genetic vulnerability increases levels of glucocorticoids with a resulting change in cellular plasticity brought about by the down regulation of growth factors and receptor sensitivity (Duman & Monteggia, 2006). The reduction in BDNF and other neurotrophic factors will have a damaging impact on the functional processes and structure of the limbic system, particularly the hippocampus. Based on this hypothesis, the successful treatment of MDD would be dependent on the reversal of these processes, for example by increasing the levels of BDNF (Maletic *et al.*, 2007).

The neurotrophic hypothesis is further strengthened by the monoamine theory of MDD, which suggests that MDD is associated with decreased levels of monoamines, especially 5-HT and NE. A high density of monoamine oxidase A (MAO-A), which is responsible for the metabolism of these monoamines (DA, NA and 5-HT), has been found in untreated depressed patients, suggesting the long-term loss of monoamines via increased MOA-A metabolism (Meyer *et al.*, 2006:1213). Specific monoamine transporter densities have a secondary effect on the level of individual extracellular monoamines; therefore, if the density for a specific monoamine transporter is low, it causes a slight increase in the extracellular monoamine and that, in turn, further increases the metabolism of the specific monoamine, resulting in depression (Meyer *et al.*, 2006). Ascending 5-HT and NE fibres originating from brainstem nuclei (i.e. raphe nucleus and locus coeruleus, respectively) innervate the limbic system with the PFC and the other structures associated with the regulation of mood. Descending pathways, on the other hand, project through the dorsal spinal column and play a vital role in pain regulation (Fields *et al.*, 1991; Meyer *et al.*, 2006). The symptoms of MDD, such as pain, mood and cognition will manifest within the overall reduction in monoamine levels, depending on the specific receptor densities within these regions (Meyer *et al.*, 2006).

Glutamate (L-Glutamic acid) has a definitive role in the development of MDD and is accepted as a key excitatory neurotransmitter in the CNS. Glutamate has various functions and it plays a major role in brain development, neuronal differentiation, axon genesis, affecting neuronal migration and neuronal survival (Coyle *et al.*, 2002; Hassel & Dingledine, 2006). It was also found to play a major role in nitrogen and carbon homeostasis, a precursor for the synthesis of the neurotransmitter GABA (specialised excitatory and inhibitory neurons) and detoxification of ammonia (Hashimoto *et al.*, 2005; Hashimoto & Hattori, 2007). Glutamate is released from presynaptic neurons and interacts with postsynaptic glutamate receptors (e.g.  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-Daspartate (NMDA) receptors and kainite). Astrocytes terminate the released glutamate via the glutamate transporter located on the presynaptic terminal. The glutamate is converted to glutamine and transported back to the presynaptic neurons where it is reconverted to glutamate (Hashimoto *et al.*, 2005; Hashimoto & Hattori, 2007). An illustration of glutamate neurotransmission is provided in Figure 2.3.



**Figure 2.3:** Schematic representation of glutamatergic neurotransmission. After the release of glutamate from the presynaptic terminal, glutamate binds to various receptors, including ionotropic (AMPA and NMDA) and metabotropic glutamate receptors. Glutamate is terminated from the synapse via the reuptake mechanism mediated by the glutamate transporter located on the presynaptic terminal as well as on astrocytes (Carlson et al., 2006).

Several studies have reported increased glutamate levels in both plasma and cerebrospinal fluid (CSF) (Kim *et al.*, 1982; Altamura *et al.*, 1993; Mauri *et al.*, 1998; Mitani *et al.*, 2006). In addition, heightened glutamate levels were confirmed by other groups (Mauri *et al.*, 1998; Mitani *et al.*, 2006). Furthermore, Mitani and colleagues (2006) found a positive correlation between plasma glutamate and the severity of depressive symptoms in MDD patients. Therefore, the increased levels of glutamate in plasma and CSF in MDD patients suggest an anomaly of the brain glial-neuronal glutamine/glutamate cycle associated with the glutamate receptor. Hyperglutamergergia has been suggested to be involved in antidepressant discontinuation syndrome (ADS) associated with non-compliance (Harvey *et al.*, 2002; Harvey *et al.*, 2003). Several studies, both clinical and preclinical, did confirm that glutamate transmission is increased following stress and plays an essential role in MDD (Gao & Bao, 2011; Harvey, 2008; Wegener *et al.*, 2010). Taking into account the 5-HT axonal glutamate pyramidal neurons in the rat's cortex (El Mansari & Blier, 1997), the discontinuation of a serotonin reuptake inhibitor (SRI) was found to promote a stress response in both humans (Michelson *et al.*, 2000) and rats (Harvey *et al.*, 2002), therefore expecting an increase in the release of glutamate and subsequent effects of cell survival and neuroplasticity (Harvey & Slabbert, 2014). The glutamate-nitric oxide (NO) system has a crucial role in both neuroplasticity and depression (Dhir & Kulkarni, 2011; Esplugues, 2002; Harvey *et al.*, 2003; Wegener *et al.*, 2010). Increased glutamate-NO levels over prolonged periods of time will eventually drive structural brain changes as observed in the hippocampus of patients with a history of chronic depression and individuals

with repeated depressive episodes (Harvey & Slabbert, 2014) (See Figure 2.2). Glutamatergic neurotransmission is increased by agonists activating (NMDA) and (AMPA) receptors on pyramidal cells mimicking a stress response in the mPFC. The activation of both NMDA and AMPA receptors in the mPFC further increases 5-HT release in the dorsal raphe, with the expected activation of 5-HT<sub>1A</sub> autoreceptors that decrease dorsal raphe serotonergic firing (Coplan *et al.*, 2014; Musazzi *et al.*, 2010). Therefore, in the mPFC, stress activates glutamatergic neurotransmission through NMDA and AMPA receptors, possibly reducing 5-HT outflow and 'flooding' the dorsal raphe (Coplan *et al.*, 2014). Glutamatergic neurotransmission is also activated by inflammation and might be adding to excessive 5-HT<sub>1A</sub> autoreceptor agonism and as a result decrease 5-HT neuron firing (Muller & Schwarz, 2007). The distinct functional changes in the brain and altered stress response mechanisms associated with non-compliance, the exposure to additional risk factors may even further harm an already vulnerable individual and lead to relapse and recurrent MDD and ultimately to TRD. Looking at this complex relation between the different cascades and mechanisms involved in the stress response, it seems to suggest that non-compliance and ADS might be precursors for the development of TRD.

One of the more exciting recent developments is the use of a sub-anaesthetic dose of ketamine to treat TRD (Rot *et al.*, 2010; Ibrahim *et al.*, 2012; Murrough, 2012; Zarate *et al.*, 2006). Ketamine is a high-affinity, non-competitive NMDA glutamate receptor antagonist (Murrough *et al.*, 2014).

### 2.2.3.3 Genetics involved in MDD

The heritability of MDD is approximately 37%, which is much lower than other mental illnesses such as bipolar disorder and schizophrenia (Kendler *et al.*, 2006). A recent study found that MDD is partly caused by heritable MDD-prone personalities, but heritable factors independent of personality may also result in MDD (Kendler *et al.*, 2006). The heritability of MDD might be higher in patients who can be linked to early onset, severity of illness and recurrent MDD (Kendler *et al.*, 1999). MDD is a common mental illness that results from a complex interplay between genes and environmental risk factors, but is also affected by other co-morbid diseases such as cardiovascular disease, cancer and diabetes mellitus (Kiyohara & Yoshimasu, 2009).

The selective 5-HT reuptake inhibitors (SSRIs) are proven to be effective in the treatment of MDD (Kato & Serretti, 2010), which makes the 5-HT system a logical source for susceptible genes to be explored. The 5-HT transporter (5-HTT) has been the focus of several studies because of its involvement in the reuptake of 5-HT at brain synapses. One common polymorphic variant of the 5-HTT-linked polymorphic region (5-HTTLPR), which affects the promoter of the 5-HTT gene, causes reduced levels of 5-HT in the presynaptic nerve terminals in the brain (Lesch *et al.*, 1996). This polymorphism confers a tendency to MDD, but also to anxiety disorders and pessimistic personalities (Belmaker & Agam, 2008; Lesch *et al.*, 1996). In another prospective epidemiologic study, Caspi and co-workers demonstrated that 5-HTTLPR predicts MDD, although only in association with defined life stressors (Caspi *et al.*, 2003).

Glutamatergic genes such as GRIK4 have been associated with the response and adverse effects of citalopram (Paddock *et al.*, 2007). Several other genes are also associated with biological mechanisms, such as the Met allele of the functional Val/Met polymorphism (rs6265) involved in the BDNF and SSRI response (Licinio *et al.*, 2009), and the BDNF single nucleotide polymorphism (SNP) that may underlie the response seen with desipramine in the treatment of MDD (Kato & Serretti, 2010; Licinio *et al.*, 2009). The genetic variation in the FK506 binding protein 5 (FKBP5), a protein involved in regulating cortisol binding to the GR (Binder, 2009), has also been associated with the effects of ADs (Lekman *et al.*, 2008). Genetic variants in the potassium channel subfamily K member 2 (TREK1), a potassium channel involved

in mediating the mechanism of action of SSRIs, is associated with non-response to several ADs (Perlis *et al.*, 2008), whereas the catechol-O-methyltransferase (COMT) gene also plays a role in AD response (Baune *et al.*, 2008; Perlis *et al.*, 2009).

Furthermore, genome-wide studies suggest that the effectiveness of ADs can be predicted by genetic markers such as corticotrophin releasing hormone (CRH) receptor-1 and CRH binding protein (CRHBP), which may predict the response to SSRIs in anxious depression (Binder *et al.*, 2010; Kupfer *et al.*, 2012; Liu *et al.*, 2007). Although multiple chromosomal regions have been identified and linked with MDD and some loci have been replicated in more than one study, no single chromosomal region has been replicated in every family genetic study linked to MDD (Belmaker & Agam, 2008). In conclusion, MDD is a mental illness with a complex pathophysiology integrating brain structures, molecular mechanisms, genes and a host of environmental risk factors, affecting people of all walks of life.

### 2.3 Current treatment for MDD

ADs are classified into six different groups, namely tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), dopamine norepinephrine reuptake inhibitors (DNRI) and atypical antidepressants (see Table 2-1).

**Table 2.1: Antidepressants registered for the treatment of MDD in adults in South Africa according to Monthly Index of Medical Specialities (Snyman, 2012)**

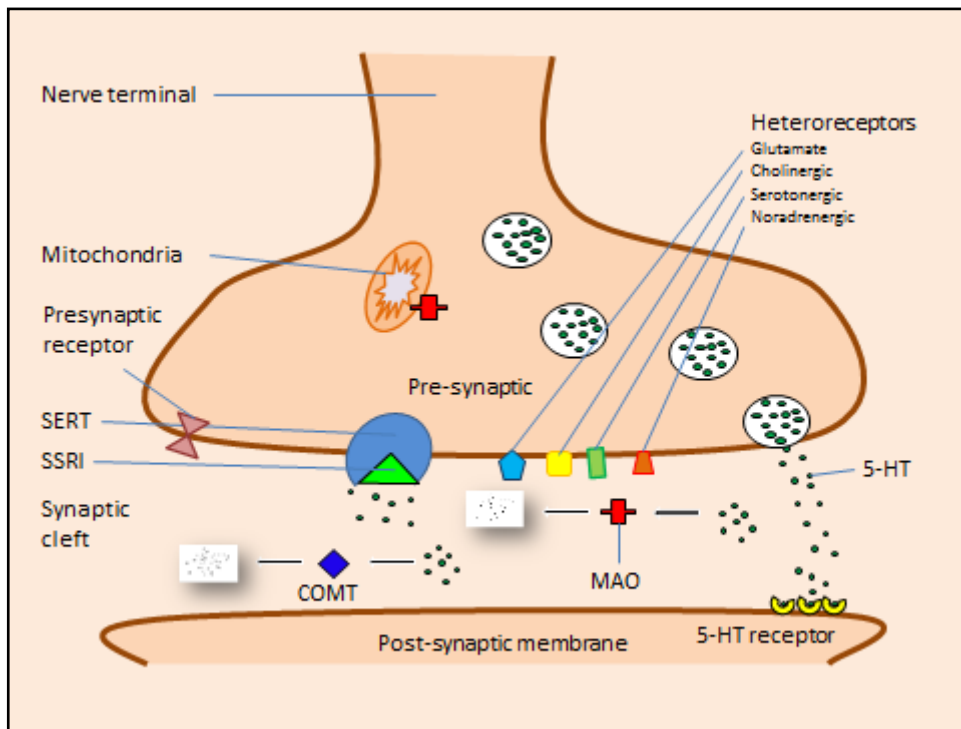
Classification	Active ingredient	Initial dose (mg/day)	Maintenance dose (mg/day)
Tricyclic antidepressants			
	Amitriptyline	25-50	100-300
	Clomipramine	75	50-100
	Dothiepin	50	50-75
	Imipramine	25-50	100-300
	Trimipramine	25-50	75-300
Serotonin reuptake inhibitors			
	Citalopram	20	20-60
	Escitalopram	10	10-20
	Fluoxetine	20	20-60
	Fluvoxamine	100	100-300
	Paroxetine	20	20-60
	Sertraline	50	50-200
Serotonin norepinephrine reuptake inhibitors			
	Duloxetine	60	60-120
	Venlafaxine	37.5	75-375
Monoamine Oxidase Inhibitors			

Classification	Active ingredient	Initial dose (mg/day)	Maintenance dose (mg/day)
	Moclobemide	150	300-600
	Tranylcypromine	10	30-60
Atypical antidepressants			
	Maprotiline	75	100-225
	Mianserine	30	30-90
	Mirtazepine	15	15-45
	Trazodone	150	150-600
Dopamine norepinephrine reuptake inhibitors			
	Bupropion	150	300-450
	Reboxetine	8	8-10

In clinical trials, patient response rates to ADs vary from 50-75%, with some studies suggesting greater efficacy vs. placebo in individuals with more severe symptoms than those with mild to moderate MDD (Fournier *et al.*, 2010; Khan *et al.*, 2002; Kirsch *et al.*, 2008). However, ADs differ in their side effect profiles, with specific side effects such as weight gain, sedation and sexual dysfunction often posing a major problem for compliance (Gelenberg *et al.*, 2010). Indeed, the issue of compliance and AD discontinuation and its impact on long-term outcome is a subject of the current study. Before an AD is prescribed, several factors must be taken into account, such as the patient's preference, efficacy of treatment, safety and tolerability of the AD, potential drug interactions, cost of medication, and co-morbid psychiatric and general illness.

### 2.3.1 Selective serotonin reuptake inhibitors (SSRIs)

The monoamine hypothesis of depression states that depression is mediated by a decrease in brain monoamine activity, in this case serotonin (5-HT) (Schildkraut, 1965). The mechanism of action for SSRIs is illustrated in Figure 2.4. In order to increase the levels of 5-HT in the synaptic cleft, an SSRI binds to the 5-HTT, preventing the reuptake of 5-HT from the synaptic cleft (Goodwin, 1996; Stahl, 1998). The blockage of the 5-HTT leads to the accumulation of 5-HT in the synaptic cleft and restores synaptic levels of 5-HT (Blier & De Montigny, 1987). However, acute administration of an SSRI increases 5-HT, often in a non-physiological manner, resulting in excessive serotonergic activity, while chronic treatment is associated with a gradual diminution over time to normal levels (Harvey, 1997). When an SSRI is bound to the 5-HTT, 5-HT is metabolised in the synaptic cleft by two enzymes, namely monoamine oxidase (MAO) and catecholamine-O-methyltransferase (COMT) (Kopin, 1985). Serotonin autoreceptors on 5-HT presynaptic terminals act to enhance the neurochemical and clinical effects of SSRIs. Heteroreceptors on the 5-HT presynaptic nerve terminal allow neurotransmitters such as glutamate, noradrenaline, dopamine and serotonin (Elhwuegi, 2004) to modulate 5-HT release (Figure 2.4) (Millan *et al.*, 2000), thereby allowing neurotransmitter cross-talk to occur. These events result in an overall increase in 5-HT in the synapse and desensitisation of the postsynaptic 5-HT serotonin receptors (Elhwuegi, 2004), eventually culminating in a cascade of actions that affect signal transduction and gene expression (Millan *et al.*, 2000).



**Figure 2.4:** The mechanism of action of the SSRIs. 5-HT is released from the terminal vesicle after which it binds to 5-HT receptors. In depression, there is a decrease in the synaptic 5-HT concentration. The SSRI binds to the 5-HTT in order to decrease the reuptake of 5-HT from the synaptic cleft and therefore increases the concentration of 5-HT in the synaptic cleft, resulting in an increased activation of postsynaptic 5-HT receptors (Adapted from CNSforum, 2011).

The following SSRIs are currently available in South Africa for the treatment of MDD: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (Snyman, 2012). The SSRIs have a superior AD response compared to placebo in the treatment of MDD (Arroll *et al.*, 2009; Gelenberg *et al.*, 2010). Numerous studies have compared the efficacy of SSRI with that of other ADs, especially the TADs, where SSRIs have demonstrated comparable efficacy but better tolerability and compliance (Anderson, 2000; Cipriani *et al.*, 2005; Hiemke & Hartter, 2000; Montgomery, 2001). Escitalopram, however, has been found to be slightly more effective in the treatment of MDD when compared to other SSRIs and venlafaxine (Kennedy *et al.*, 2006).

### 2.3.1.1 Adverse effects associated with SSRIs

Although ADs may differ slightly in efficacy, tolerability plays a determining role in a successful outcome. Each class of AD has a different adverse effect profile that must be taken into account when prescribed, while within-class differences are also apparent and need to be considered (Harvey, 1997). Drug interaction risk plays a very important part in the selection criteria of the appropriate antidepressant (Van den Berg, 1995). Pharmacokinetic factors (half-life and effect on CYP450 enzyme) must also be taken into account, especially within the SSRI class (Harvey, 1997), since these characteristics play a major role in metabolism and drug interactions (Hiemke & Hartter, 2000). The half-life of antidepressants is an essential factor in the prediction of discontinuation syndrome, as AD with a short half-life is more prone to cause antidepressant discontinuation syndrome (ADS) and leads to further

poor compliance (Haddad & Anderson, 2007). In section 2.3.3, there is a more detailed discussion regarding ADS and antidepressant compliance.

At the start of treatment, SSRIs commonly cause serotonergic side effects, such as nausea, vomiting and diarrhoea, in a dose-dependent manner, which usually subside after the first week (Kam & Chang, 1997). In some patients, the diarrhoea might persist (Edwards & Anderson, 1999). SSRIs sometimes cause increased restlessness, agitation, insomnia and anxiety (Snyman, 2012) that also tend to decrease over time (Harvey, 1997). Anxiety at the start of treatment might be reduced by starting with a low dose and gradually increasing it over time (Harvey, 1997). Akathisia has also been linked to the use of SSRIs and can contribute to the occurrence of restlessness and agitation (Caley, 1997). The insomnia associated with SSRIs is also a serotonergic effect brought on by altered sleep architecture, and can be treated with either cognitive behavioural therapy CBT, or adding a sedative hypnotic drug or trazodone to the regimen (Gelenberg *et al.*, 2010).

Although sexual dysfunction is associated with most ADs, it seems to be more frequent in patients using SSRIs (Gelenberg *et al.*, 2010). The sexual side effects include erectile or ejaculatory dysfunction in men, whereas anorgasmia and loss of libido are experienced in both sexes. There may also be several contributing causes for sexual dysfunction, including the underlying MDD, disturbance in the relationship, sexual dysfunction as a co-morbid disorder, or need for sexual education. It is therefore up to the prescribing psychiatrist to establish the underlying cause and the best course of action in addressing it (Gelenberg *et al.*, 2010). In some cases, the dysfunction disappears with time, while lowering the daily dosage or changing to another AD such as bupropion is recommended in some patients (Walker *et al.*, 1993). However, in most patients, this side-effect remains unchanged (Gelenberg *et al.*, 2010) and in many instances results in noncompliance. A number of pharmacologic treatment strategies are available if it is determined that the SSRI is responsible for sexual dysfunction, including the addition of buspirone (Landen *et al.*, 1999), bupropion (Clayton *et al.*, 2004), sildenafil (Nurnberg *et al.*, 2003) or tadalafil (Segraves *et al.*, 2007).

As a central nervous system (CNS) drug, and given the diffuse distribution of 5-HT in the brain, SSRIs can have numerous neurologically adverse effects. At the start of treatment, SSRIs may aggravate both tension and migraine-related headaches, although this adverse effect tends to be short lived and improves within a few weeks. On the other hand, chronic SSRI treatment may prevent migraine headaches (Doughty & Lyle, 1995; Hamilton & Halbreich, 1993). Some studies have linked SSRIs to extrapyramidal effects such as akathisia, dystonia, tardive dyskinesia and Parkinsonism (Gerber & Lynd, 1998; Leo, 1996), and is proposed to be due to 5-HT-mediated suppression of DA release in the striatum (Harvey, 1997). Though the incidence of these adverse effects is rare, it may be higher in older patients, especially in patients with Parkinson's disease (Gelenberg *et al.*, 2010).

Only certain SSRIs are associated with weight gain, which may be substantial in some patients (Papakostas, 2007). Weight loss is associated with short-term treatment with fluoxetine (Ferguson & Feighner, 1987), although weight gain has emerged as a common adverse effect with chronic SSRI therapy (including fluoxetine, sertraline and paroxetine) (De Wilde *et al.*, 1993; Ferguson, 2001). Various mechanisms for this response have been proposed (see review by (Harvey & Bouwer, 2000). Paroxetine has the highest incidence of this side effect compared to the other SSRIs (Edwards & Anderson, 1999; Fava *et al.*, 2000), whereas fluoxetine may cause an initial reduction in weight that later on normalises with chronic treatment (Michelson *et al.*, 1999).

### 2.3.1.2 Pharmacokinetics of SSRI's

The SSRIs have variable effects on hepatic microsomal enzymes and therefore have increased potential for drug-drug interactions. Both fluoxetine and paroxetine are strong inhibitors of the CYP 2D6 isoenzyme (Harvey, 1997). When administered with tamoxifene (treatment for breast cancer), the metabolism of the active metabolite of tamoxifene, endoxifen, is decreased (Desmarais & Looper, 2009; Stearns *et al.*, 2003) with an increased likelihood of breast cancer relapse (Kelly *et al.*, 2010). The drug-drug interaction between SSRIs and MOAI can be potentially fatal as a result of serotonin syndrome (see section 2.2.3.2) (Gelenberg *et al.*, 2010). When a patient switches from fluoxetine to tranylcypromine, there is a need for a minimum washout period of at least five weeks; whereas, for the other SSRIs, approximately two weeks washout period is needed to avoid serotonin syndrome (Beasley *et al.*, 1993; Gelenberg *et al.*, 2010).

ADS is increasingly being seen as a major contributor to non-compliance as well as worsening the long-term outcome of depression and its treatment (see for review Harvey *et al.*, 2003; Harvey & Slabbert, 2014), and is in fact a major focus of this study. An antidepressant's pharmacodynamic and pharmacokinetic profile is a reliable predictor of ADS risk. For the most, ADS symptoms are closely associated with the sudden discontinuation of antidepressants with a short half-life (Baldwin *et al.*, 2007), such as paroxetine, sertraline (Thompson, 1998), venlafaxine (Agelink *et al.*, 1997), mirtazapine (Berigan, 2001), trazodone (Peabody, 1987), and duloxetine (Warner *et al.*, 2006) (Table 2.2). Norfluoxetine is an active metabolite of fluoxetine with a plasma half-life of up to nine days (Harvey, 1997), as fluoxetine is renowned as the SRI with the lowest incidence of ADS (Tint *et al.*, 2008). In fact, fluoxetine is often one of the antidepressants used for the treatment of SRI-induced ADS. Nevertheless, the antidepressant's half-life cannot always be taken as an absolute predictor of ADS. Price and co-workers (1996) reported that with paroxetine, a patient has a 10 times higher risk of developing ADS when compared to patients taking fluvoxamine (Price *et al.*, 2003), despite both SRIs having similar half-lives (Table 2.2). The latter aspect is a focus of a recent review paper (Harvey & Slabbert, 2014) and forms an integral part of this study.

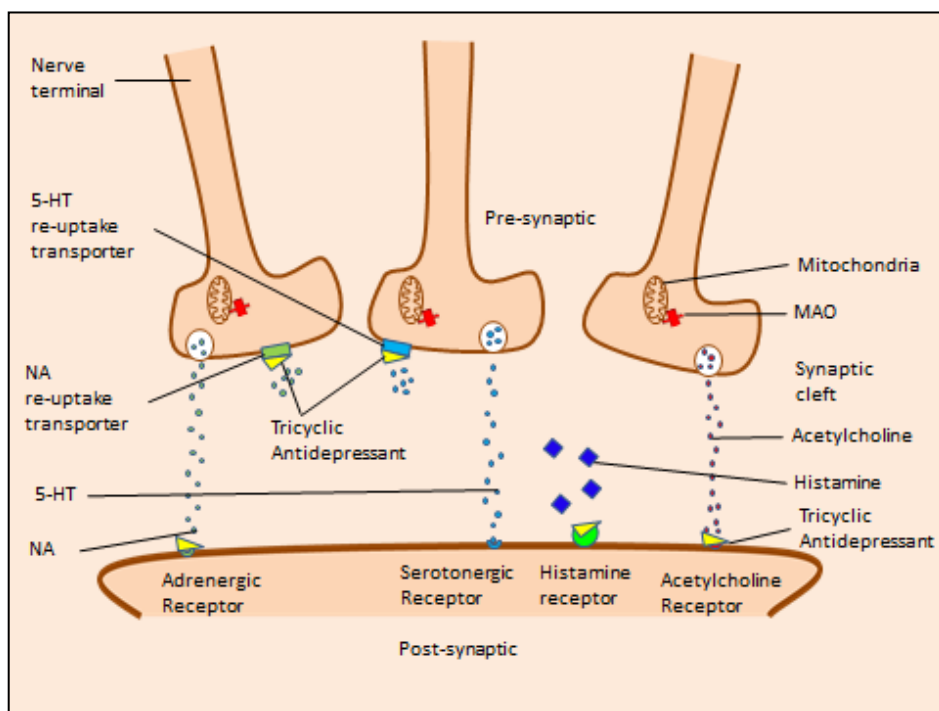
**Table 2.2: Half-life (T<sub>1/2</sub>) of selected antidepressants**

Drug	Half live (hours)
Agomelatine	2.5
Duloxetine	11-16
Fluoxetine	96-216
Mirtazapine	20-40
Paroxetine	21
Sertraline	26
Trazodone	7.1
Venlafaxine	3-13
Tricyclic antidepressants	24-36

### 2.3.2 Tricyclic Antidepressants (TCAs)

In South Africa, the following tricyclic antidepressants (TCAs) are used for the treatment of MDD: amitriptyline, clomipramine, dothiepin, imipramine, lofepramine and trimipramine (Snyman, 2012). The efficacy of TCAs is comparable to other classes of ADS, including SNRIs, SSRIs and MOAIs (Anderson, 2000). The TCAs are especially effective in hospitalised patients, with at least one study suggesting that slightly more patients make a recovery after being treated with amitriptyline compared to SSRIs, although they are less well tolerated than SSRIs (Barbui & Hotopf, 2001). The TCAs have shown an improved response vs. SSRIs in patients with melancholia and severe depression, although this specific advantage has not been consistently documented in less severely ill patients (Anderson, 2000; Barbui & Hotopf, 2001).

In Figure 2.5, the mechanism of the TCAs displays how the TCAs inhibit the reuptake of both NA and 5-HT by blocking both the noradrenaline and serotonin reuptake transporters. This action leads to an overall increase in monoamine concentrations in the synaptic cleft. The down-regulation of post synaptic receptors and the ensuing changes in gene expression are responsible for the AD effects of the TCAs (Ciraulo *et al.*, 2011). The TCA class of antidepressants is associated with many unwanted side effects, which may be attributed to their multi-receptor actions at histamine (H<sub>1</sub>), muscarinic and  $\alpha$ -adrenergic receptors (Ciraulo *et al.*, 2011).



**Figure 2.5:** The mechanism of action of the TCAs is illustrated. The TCAs bind to the 5-HT and NA reuptake transporters presynaptically to increase the amount of monoamines in the synaptic cleft. In this figure, the amount of histamine is shown to increase due the blockade of histamine receptors, which is associated with sedation as a side effect of the TCAs. Furthermore, the blockade of muscarinic and  $\alpha$  adrenergic receptors is also associated with the side effects experienced by patients (adapted from CNSforum, 2011).

### 2.3.2.1 Adverse effects associated with TCAs

The TCAs have outspoken cardiovascular side effects, including arrhythmias, tachycardia and orthostatic hypotension. Therefore, electrocardiography (ECG) is indicated before starting a TCA, especially in elderly patients and those with a significant cardiac risk (Joo *et al.*, 2002; Miller *et al.*, 1998). TCAs increase the threshold for excitation by depressing fast sodium channels, prolong cardiac cell action potentials through action on potassium channels, and prolong cardiac refractoriness through actions on both types of channels – the mechanism of action followed by the class Ia antiarrhythmic drugs such as procainamide and quinidine (Roden, 2006). Consequently, TCAs in combination with class I antiarrhythmic drugs are contraindicated as it can exert an additive toxic effects on an already precarious cardiac condition. During TCA overdose, serious arrhythmias can occur, which may be fatal (Thanacoody & Thomas, 2005).

All TCAs are associated with anticholinergic side effects such as constipation, tachycardia, sexual dysfunction, blurred vision and urinary hesitation (Gelenberg *et al.*, 2010). Some patients develop a certain degree of tolerance to the anticholinergic side effects, but in other patients additional treatment is required to overcome these symptoms. The anticholinergic profile is one of the main reasons for the poor treatment compliance rates associated with TCAs (Preskorn & Jerkovich, 1990). In elderly patients, TCAs can lead to memory impairment, decreased concentration and in some cases anticholinergic delirium in the medically compromised and in individuals already using other anticholinergic drugs. These symptoms are usually associated with high TCA blood levels, which can be addressed by lowering the prescribed daily dosage (Preskorn & Jerkovich, 1990).

The TCAs have an affinity for both muscarinic and histaminergic receptors, which are responsible for causing sedation. In most cases, sedation decreases after the first week of treatment, although it can persist for longer. Patients should be encouraged to allow some time to pass before changing to another non-sedative antidepressant (Baldessarini, 2006). However, these adverse effect might be useful in patients suffering from co-morbid insomnia, in which case they take their medication before bedtime (Gelenberg *et al.*, 2010).

TCAs also cause weight gain, which is potentially reversible once the AD is discontinued (Nihalani *et al.*, 2011). It has been suggested that weight gain is due to combined anti-histaminergic and anti-serotonergic actions of TCAs (blockade of 5-HT<sub>2</sub> receptors) (Deshmukh & Franco, 2003).

At high dosage, TCAs can cause myoclonus, in which case the dosage should be lowered (Garvey & Tollefson, 1987). Myoclonus usually does not occur at lower dosages or therapeutic levels (Evidente & Caviness, 1999). An overdose of TCA may also cause seizures (Ruffmann *et al.*, 2006).

### 2.3.2.2 Drug interactions associated with TCAs

TCAs are metabolised by hepatic microsomal enzymes, which makes this class of AD susceptible to drug interactions, especially with drugs that inhibit or induce hepatic microsomal enzymes (Gelenberg *et al.*, 2010). Therefore, drugs that induce CYP 3A4, such as carbamazepine and barbiturates, will decrease the blood concentrations of TCAs. On the other hand, perphenazine, fluoxetine and paroxetine will cause a rise in TCA blood levels by inhibiting CYP 2D6 (Harvey, 1997). Furthermore, TCAs can also reduce the blood levels of valproate and lower the activity of clonidine (Perry *et al.*, 1994). Potentially lethal interactions exist between TCAs and MOAI, which may lead to hypertensive crisis and the 5-HT syndrome (Gelenberg *et al.*, 2010).

### 2.3.3 Monoamine oxidase inhibitors (MAOIs)

Although phenelzine, tranylcypromine, isocarboxazid and moclobemide are available elsewhere, only tranylcypromine (a non-selective MAOI) and moclobemide (a reversible selective MAOI-A) are registered in South Africa for the treatment of MDD (Snyman, 2012). Although there is no difference in the efficacy between MAOI and other ADs, this class of AD has been suggested to be effective in MDD patients as a last resort following therapeutic failure to the first- and second-line ADs (i.e. SSRIs, SNRIs and TCAs) (Thase *et al.*, 1995). MAOIs have also been found to be effective in MDD patients with atypical symptoms, such as reactive mood and hyperphagia (Henkel *et al.*, 2006; Thase *et al.*, 1995).

There are several mechanisms of action that contribute to the AD effect of the MAOIs. These include the inhibition of the metabolism of brain biogenic amines (NA, 5-HT and DA) as well as trace amines, for example tyramine, octopamine and phenylethylamine.

#### 2.3.3.1 Adverse effects associated with MAOI

The use of MAOIs is commonly linked to cardiovascular side effects, such as hypotension and peripheral oedema (Gelenberg *et al.*, 2010). Similar to the other ADs, MAOIs are associated with weight gain (Amsterdam & Bodkin, 2006). MAOIs also cause sexual dysfunction, particularly decreased libido, erectile/ejaculatory dysfunction and anorgasmia (Waidinger & Olivier, 1998). Sexual side effects usually subside after a few weeks of treatment. In some cases, sexual dysfunction may be linked to a high dosage. The MAOIs are also linked to neurological side effects such as myoclonic jerks, daytime drowsiness and sedation (Remick & Froese, 1990).

#### 2.3.3.2 Drug and food interactions associated with MAOI

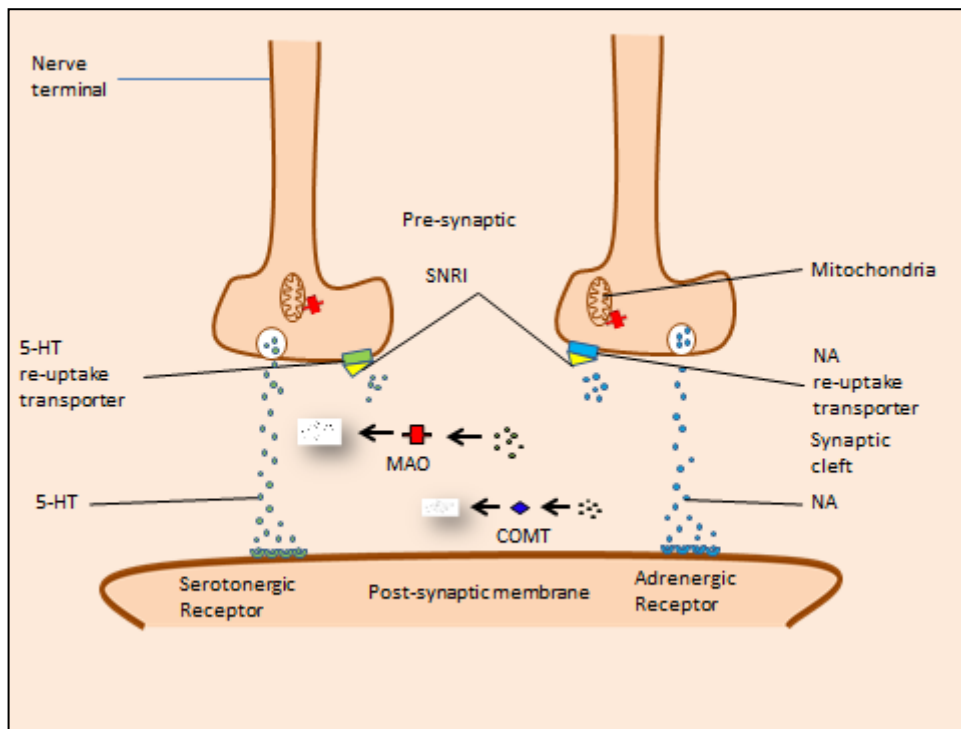
A possible lethal interaction exists between non-reversible MAOI (e.g. tranylcypromine) and tyramine-rich foods (e.g. aged cheeses or meats, fava or broad beans, red wine, caviar and yeast extracts) and other vasoactive amines (e.g. ephedrine, phenylethylamines), which can lead to a hypertensive crisis (Gardner *et al.*, 1996; Rapaport, 2007). A hypertensive crisis is characterised by the acute onset of nausea, neck stiffness, severe headaches, palpitations, perspiration, confusion, with an increased risk of stroke and death (Thase *et al.*, 1995). Several drugs, including SNRIs, TCAs, sympathomimetic vasoconstrictive agents and over the counter (OTC) decongestants, can produce a hypertensive crisis when taken in combination with MAOIs (Rapaport, 2007; Stahl & Felker, 2008). Dietary restrictions, however, are unnecessary when taking moclobemide, which is a reversible selective monoamine oxidase-A inhibitor (Gelenberg *et al.*, 2010). Monoamine oxidase-A (MAO-A) is one of the enzymes that metabolise monoamines such as 5-HT, NA, DA and tyramine (Youdim *et al.*, 2006). Moclobemide has a distinct advantage over tranylcypromine, because it is a reversible inhibitor of MAO-A, while tranylcypromine is an irreversible MAO-A inhibitor. Since MAO-A is irreversibly inhibited by tranylcypromine, there is a significant increase in the concentration of monoamines. However, since the MAO-A is irreversibly inhibited, the body must regenerate MAO-A in order for to normalise enzyme activity, which can take several weeks. Therefore, although tranylcypromine has been eliminated from the body, the MAO inhibition persists (Mallinger & Smith, 1991).

Serotonin syndrome is triggered by excessive CNS serotonergic activity and presents with diarrhoea, flushing, hyperthermia, abdominal pain, lethargy, tremor, myoclonus, cardiovascular shock, renal failure and possibly death (Boyer & Shannon, 2005). The syndrome is closely associated with all classes of MAOIs when taken with serotonergic drugs such as SSRIs and buspirone (Stahl & Felker, 2008;

Sternbach, 1991). There are a number of drugs that can also cause 5-HT syndrome when taken with MAOIs, for example synthetic opioids (dextromethorphan, meperidine, tramadol, propoxyphene, methadone), non-AD tricyclic compounds (carbamazepine, cyclobenzaprine), sibutramine and OTC drugs (chlorpheniramine) (Stahl & Felker, 2008). Serotonin syndrome is also a risk in patients taking SSRIs in combination with tramadol (inhibit the serotonin reuptake), high-dose tryptans used to treat migraine (postsynaptic serotonin receptor agonist) and linezolid (inhibit serotonin's metabolism) (Gillman, 2005; Huang & Gortney, 2006; Sola *et al.*, 2006).

#### **2.3.4 Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)**

In South Africa, there are only two registered SNRIs available, namely venlafaxine and duloxetine (Snyman, 2012), whereas desvenlafaxine (the primary metabolite of venlafaxine) is approved in the United States of America (USA) to treat MDD (Gelenberg *et al.*, 2010). Venlafaxine is available in an extended release (XR) formulation, which is preferred because it allows for once-a-day dosing, thereby increasing patient compliance and reducing the possibility of ADS (Gelenberg *et al.*, 2010). Individual studies with venlafaxine and duloxetine have reported that SNRIs are, in general, as effective as SSRIs in the treatment of MDD (Nemeroff *et al.*, 2008). However, a meta-analysis conducted by Einarson and co-workers found that venlafaxine XR is clinically superior to SSRIs and TCAs and slightly (but not significantly) better tolerated (Einarson *et al.*, 1999). Another meta-analysis suggested a small advantage for SNRIs relative to SSRIs (Bauer *et al.*, 2009), which might offer a moderate clinical benefit in patients with more severe MDD (Thase *et al.*, 2007) or in patients who do not respond to SSRIs (Papakostas *et al.*, 2008a). At a higher dosage (75-375mg per day), venlafaxine has displayed a significant difference in response rates (71%) when compared to SSRIs (64%) over a period of eight weeks (Stahl *et al.*, 2002). In this study, venlafaxine also displayed a faster onset of action in comparison with SSRIs. In a meta-analysis, Bauer and co-workers found that SNRIs might have a slightly higher remission rate than that of the SSRIs (Bauer *et al.*, 2009), although a large number of articles have questioned this (Cipriani *et al.*, 2005; Gartlehner *et al.*, 2008; Kennedy *et al.*, 2006; Panzer, 2005). The better response rates and faster onset of action at higher dosages are thought to be due to the dual action of venlafaxine, as illustrated in Figure 2-4, whereby the reuptake of primarily serotonin is inhibited at a lower doses (below 225mg) and the reuptake of both serotonin and noradrenalin is inhibited at higher doses (Horst & Preskorn, 1998; Stahl *et al.*, 2002). Therefore, the dual action of venlafaxine may explain the superiority over mono-action SSRIs (see Figure 2.6). Furthermore, venlafaxine possesses a weak affinity for DA receptors (Holliday & Benfield, 1995) and rapidly down-regulates  $\beta$  adrenergic receptors (Ciraulo *et al.*, 2011). Duloxetine is presumed to have a similar mechanism of action to that of venlafaxine, but with duloxetine displaying a greater potency at the noradrenergic reuptake transporter (Ciraulo *et al.*, 2011).



**Figure 2.6:** The mechanism of action of the SNRIs. The SNRI class of ADs blocks both the 5-HT and NA reuptake transporter in order to increase the total amount of monoamine in the synaptic cleft and to restore the monoamine balance (adapted from CNSforum, 2011).

#### 2.3.4.1 Adverse effects associated with SNRIs

The adverse effects of SNRIs are very similar to those experienced with SSRIs, such as nausea, sexual dysfunction and psychomotor activation. Most of these adverse effects subside with continuous use of the SNRI. SNRIs are also linked to adverse effects related to noradrenergic activity, including dry mouth, dilated pupils, sweating, increased pulse rate and constipation (Gelenberg *et al.*, 2010). The SNRIs are associated with an increased risk for hypertension, especially venlafaxine in doses above 150mg/day (Thase, 1998), a dose most often used in treatment resistant MDD (TRD). Although duloxetine and desvenlafaxine have a lower risk for hypertension, high dosages (60-120mg/day) of duloxetine (Thase *et al.*, 2005b) and 50-100mg/day of desvenlafaxine (Clayton *et al.*, 2009) may also cause hypertension. The hypertension risk with SNRIs is controlled by reducing the dosage. However, in well-controlled MDD patients, it might be advisable not to change the AD dosage, but rather to add an antihypertensive drug (Gelenberg *et al.*, 2010). An SNRI combination with MAOIs can also lead to a potentially fatal 5-HT syndrome (Snyman, 2012).

#### 2.3.5 Other antidepressants

The following ADs differ in structure and pharmacological action, and do not fit in with the aforementioned four antidepressant classes.

### 2.3.5.1 Bupropion

Bupropion is classified as an NA-DA reuptake inhibitor, and therefore a dopaminergic/noradrenergic AD. However, this effect is relatively weak and its exact mechanism of action is not yet fully understood (Fava *et al.*, 2005). An important difference between bupropion and other ADs is that it is not indicated for MDD associated with anxiety (Papakostas *et al.*, 2008c) and does not have the typical sexual side effects associated with other classes of AD (Thase *et al.*, 2005a). Unlike SSRIs and SNRIs, bupropion is devoid of serotonergic side effects. SSRIs are slightly superior to bupropion in the treatment of MDD with co-morbid anxiety (Papakostas *et al.*, 2008c). In the same meta-analysis, they found that in patients with no or low levels of anxiety, bupropion had a comparable efficacy to SSRIs in the treatment of MDD (Papakostas *et al.*, 2008c). Bupropion was also found to improve sleepiness and fatigue associated with MDD, and for this purpose it is superior to the SSRIs (Papakostas *et al.*, 2006). Another indication for bupropion is to assist patients to quit smoking, by reducing the desire for nicotine (Gelenberg *et al.*, 2010; Hughes *et al.*, 2007). This mechanism has been ascribed to the fact that bupropion appears to be working on several brain pathways connected to dependence, including the inhibition of both NA and DA transporters (Ascher *et al.*, 1995) and antagonism at nicotinic acetylcholine receptors (Slemmer *et al.*, 2000). Patients using bupropion tend to gain minimal weight or in some cases even lose weight, which makes bupropion appropriate to treat overweight depressed patients (Li *et al.*, 2005).

#### 2.3.5.1.1 Adverse effects associated with bupropion

Some of the most common adverse effects caused by bupropion include jitteriness, agitation, gastrointestinal upset and insomnia (Gelenberg *et al.*, 2010).

### 2.3.5.2 Trazodone

Apart from the TCAs, trazodone is one of the oldest ADs still in use today. Trazodone is a triazolopyridine derivative and exerts a dual mechanism of action via inhibition of the 5-HT<sub>2A</sub> receptor (Stahl, 2009) and inhibition of the 5-HTT (Fagiolini *et al.*, 2012). The dual action is dose dependent. At a low dose, trazodone blocks 5-HT<sub>2A</sub> receptors as well as H<sub>1</sub> and  $\alpha$ -adrenergic receptors, being responsible for its hypnotic effect. At a much higher dosage, trazodone blocks the 5-HTT, which leads to an increase in 5-HT concentrations in the synaptic cleft, rendering trazodone its AD properties (Stahl, 2009). Furthermore, at the high dose (150-600mg per day) needed for its AD action, trazodone also acts as an antagonist on both  $\alpha_2$  adrenergic and 5-HT<sub>2C</sub> receptors. The blockade of 5-HT<sub>2C</sub> receptors enhances trazodone's AD effect, a mechanism shared by several antidepressants (TCAs, agomelatine, mirtazapine) (Millan, 2005). In recent years, it has seen widespread use as a sedative hypnotic rather than an AD; however, it is an effective AD (Cunningham *et al.*, 1994). Fagiolini and co-workers reported that trazodone is a well-tolerated and effective treatment option for MDD, while avoiding the negative effects on sleep, sexual function, anxiety, as seen with SSRIs (Fagiolini *et al.*, 2012). Because of its 5-HT<sub>2A</sub> receptor blocking effects, its range of serotonergic side effects is less than that of the SSRIs (Fagiolini *et al.*, 2012). Trazodone is effective in both mono-therapy and in combination therapy in the treatment of MDD (Fagiolini *et al.*, 2012).

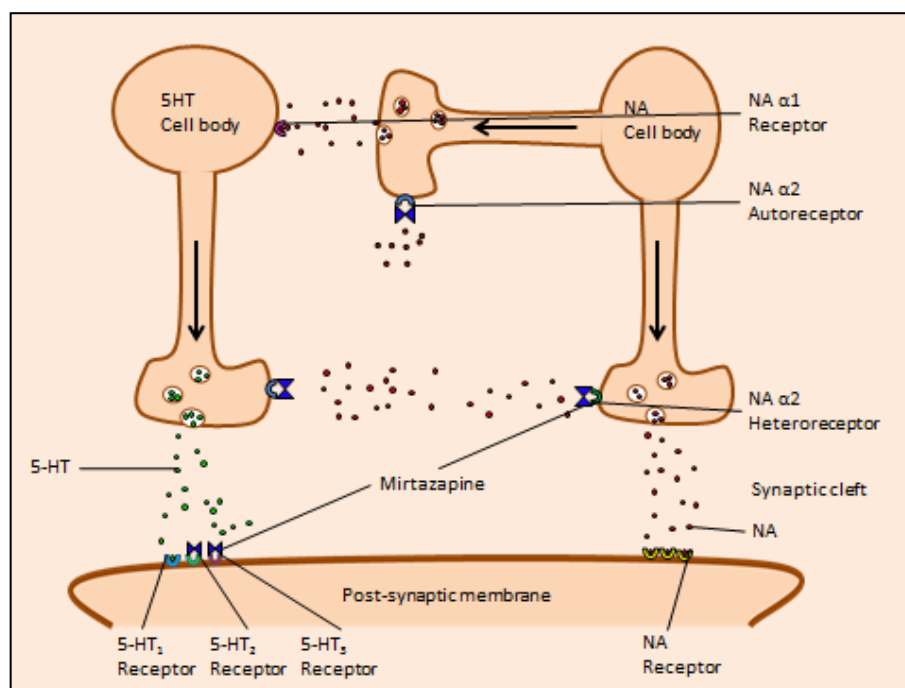
#### 2.3.5.2.1 Adverse effects associated with trazodone

Sedation is one of the common adverse effects of trazodone (Gartlehner *et al.*, 2008), although this may more often be an advantage in MDD associated with insomnia and agitation (Mendelson, 2005). Other

side effects linked to the use of trazodone include orthostasis, life threatening ventricular arrhythmias (Mendelson, 2005), erectile dysfunction and in rare cases priapism (Jayaram & Rao, 2005; Thompson *et al.*, 1990). Priapism is a medical condition where the patient suffers from prolonged penile erection (often painful and potentially harmful), usually lasting for longer than four hours, caused by a dysfunction of mechanisms controlling rigidity, flaccidity and tumescence of the penis (Broderick *et al.*, 2010). Trazodone has a high affinity for  $\alpha_1$  adrenoceptors and a slight affinity for  $\alpha_2$  adrenoceptors, resulting in the blocking of adrenoceptors responsible for these side effects (Krege *et al.*, 2001).

### 2.3.5.3 Mirtazapine

It has been suggested that mirtazapine works via mechanisms that involve both serotonergic and noradrenergic neurotransmission through the potent and direct blocking of  $\alpha_2$  adrenergic auto- and heteroreceptors (de Boer, 1996). The potent and direct blocking of  $\alpha_2$  adrenergic auto- and heteroreceptors results in increased noradrenergic transmission, which stimulates  $\alpha_1$ -adrenergic receptors on the serotonergic cell body as depicted in Figure 2.7. The blockade of  $\alpha_2$  adrenergic heteroreceptors situated on the 5-HT nerve terminal stops this receptor from turning off the increased serotonin activity (de Boer, 1996). Serotonergic transmission is slightly enhanced by mirtazapine, a weak agonist at the 5-HT<sub>1A</sub> receptor (de Boer *et al.*, 1988). Mirtazapine has only limited serotonergic side effects because of its ability to inhibit 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors post-synaptically, which may also play a role in the hypnotic and anxiogenic effects of the drug (Ciraulo *et al.*, 2011). Mirtazapine is also known as a noradrenergic and specific serotonergic antidepressant (NASSA), although it is not a monoamine reuptake inhibitor (Artigas *et al.*, 2002). The efficacy of mirtazapine is comparable with the SSRIs in the treatment of MDD (Papakostas *et al.*, 2008b).



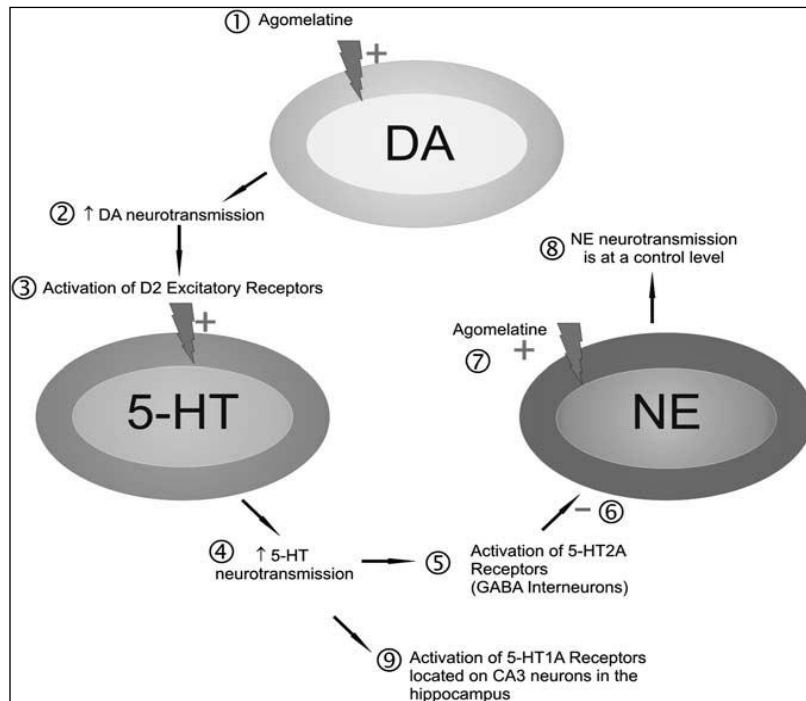
**Figure 2.7:** The mechanism of action of mirtazapine. Mirtazapine has a dual mechanism of action that increases the concentration of 5-HT and noradrenaline in the synaptic cleft. NASSAs bind to and inhibit both noradrenaline  $\alpha_2$ -autoreceptors and noradrenaline  $\alpha_2$ -heteroreceptors. This action prevents the negative feedback effect of synaptic noradrenaline on 5-HT and noradrenaline neurotransmission, and neurotransmission sustained. NaSSAs also block 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors on the

**post-synaptic membrane, which causes enhanced 5-HT<sub>1</sub>-mediated neurotransmission (CNSforum, 2011).**

Due to its actions at muscarinic (mACh) receptors, mirtazapine is associated with dry mouth and sedation, whereas the interaction with H<sub>1</sub> receptors may cause sedation and weight gain (Ciraulo *et al.*, 2011). Most of these symptoms only occur at the start of the treatment, although weight gain is greater than that experienced with MAOIs and SSRIs (Gartlehner *et al.*, 2008). Less common adverse effects of mirtazapine include an increase in cholesterol serum levels (Davis & Wilde, 1996) and agranulocytosis (Szegedi & Schwertfeger, 2005).

#### **2.3.5.4 Agomelatine**

Agomelatine is the first approved non-monoaminergic AD that exerts its AD effect through the melatonergic system (de Bodinat *et al.*, 2010). Several studies also suggest that agomelatine is effective in the treatment of general anxiety disorder (GAD) (Green, 2011; Stein *et al.*, 2008). Agomelatine acts as an agonist at melatonergic (MT<sub>1</sub> and MT<sub>2</sub>) receptors and as an antagonist at 5-HT<sub>2C</sub> receptors (Millan *et al.*, 2003) that allow it to re-entrain altered circadian rhythms known to be central to the underlying pathology of MDD. Millan and co-workers also found that the blockade of the 5-HT<sub>2C</sub> receptor by agomelatine leads to the disinhibition of dopaminergic and noradrenergic neurotransmission in the frontal cortex that it also seen as being central to its antidepressant effects (Millan *et al.*, 2003) as well as its anxiolytic actions (Kasper & Hamon, 2009) (see Figure 2.8). Agomelatine is unique in that it does not induce an acute elevation in 5-HT so that patients are not troubled by serotonergic side effects, such as agitation, insomnia, sexual dysfunction, anxiety, nausea etc.



**Figure 2.8:** Illustration of the effect of chronic agomelatine treatment on the monoaminergic system. . (1) After 14 days, agomelatine induces an excitatory effect on DA cells in the ventral tegmental area (VTA), (2) causing an increase in DA neurotransmission (3) leading to the activation of excitatory D2 receptors. (4) An increase in 5-HT firing (5) induces the activation of excitatory 5-HT2A receptors in the GABA interneurons. (6) The increase in GABA activity inhibits the locus coeruleus noradrenaline (LC-NA) neurons. (7) Acute agomelatine (2 days) treatment also exerts an excitatory effect on the LC-NA neurons. The (4) increase in 5-HT firing induces the (9) activation of inhibitory postsynaptic 5-HT1A receptors that may contribute to a decrease in the hyperactivity of the hippocampus frequently detected in MDD patients (Chenu et al., 2013).

From a pharmacokinetic point of view, agomelatine is extensively metabolised by cytochrome P450, isoforms 1A1, 1A2 and 2C9, thereby displaying a relatively low bioavailability, although retaining robust *in vivo* activity in humans and animals (de Bodinat *et al.*, 2010; Fornaro *et al.*, 2010). The compound has a moderate volume of distribution (35 L), is 85-95% bound to plasma proteins (Fornaro *et al.*, 2010), is eliminated mainly by urinary excretion (Dolder *et al.*, 2008) and has a half-life of 2.5 hours (de Bodinat *et al.*, 2010; Dolder *et al.*, 2008). Its major metabolite, 3-hydroxy-7-desmethyl-agomelatine, has a low affinity for MT<sub>1</sub>, MT<sub>2</sub> and 5-HT<sub>2C</sub> receptors.

One of the main advantages of agomelatine, and contrary to what may be expected given its short half-life, is the fact that it is not associated with ADS (de Bodinat *et al.*, 2010). In fact, this unique attribute is a focus of a review paper that forms part of the objectives of this study (Harvey and Slabbert, 2014). Furthermore, a study by Lam found that the onset of action for agomelatine was marginally superior to that of both SSRIs and SNRIs (Lam, 2010). Agomelatine also demonstrated AD efficacy in poor responders or those unresponsive to SSRIs (Kasper & Hajak, 2013). Agomelatine, unlike SSRIs, also has a

favourable effect on anhedonia in MDD (Kennedy, 2012:865) and does not induce cognitive blunting (Kennedy, 2012:866). Lastly, due to agomelatine's favourable side effect profile and proven antidepressant efficacy, it is a good alternative to other ADs in difficult-to-treat patients and can also be used as a first-line treatment in MDD patients.

#### 2.3.5.4.1 Adverse effects associated with agomelatine

Agomelatine seems to have a very limited side effect profile, causing no weight gain or sexual dysfunction, and which might be one of the reasons why agomelatine has a lower discontinuation rate when compared to other classes of ADs (Demyttenaere, 2011). Some of the most common side effects include dizziness, gastric disturbances, headaches and tiredness. Liver damage, usually reversible, is seen particularly in patients with a history of liver disease (de Bodinat *et al.*, 2010).

## 2.4 Problems related to the use of antidepressant drugs

### 2.4.1 Duration of AD treatment for depression

In the current literature there are several inconsistencies/confusions regarding the duration of AD treatment. In the next section, we will discuss the treatment guidelines for the optimum treatment period needed to achieve and remain in remission. The guidelines referred to in this section were developed by an international task force for the World Federation of Societies of Biological Psychiatry (WFSBP) based on the latest research and internationally accepted guidelines (Bauer *et al.*, 2013). Furthermore, the treatment duration can be divided into three phases of treatment according to the treatment period and will be illustrated in Figure 2.9 (Bauer *et al.*, 2013). The first treatment phase is known as the acute phase; then, a patient enters the continuation phase, and the last phase of treatment is the maintenance phase.

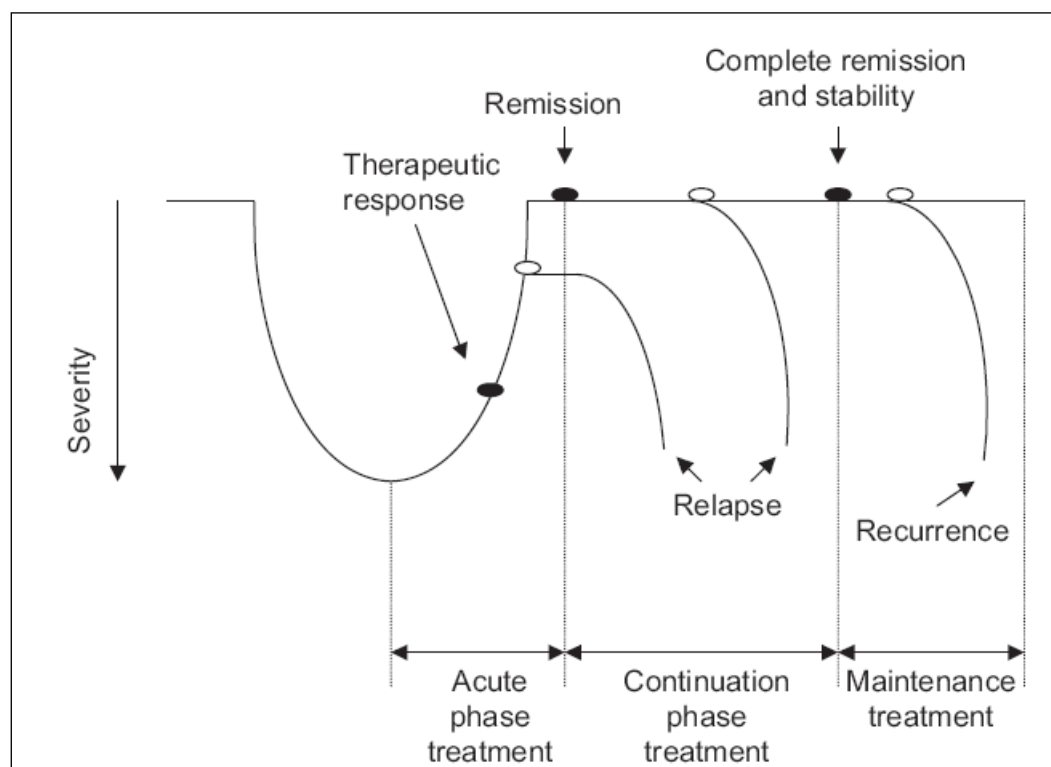


Figure 2.9: A schematic illustration of the treatment and phases of MDD (Bauer *et al.*, 2013)

As mentioned above, the acute phases include the first 12 weeks of treatment with the ultimate objective to achieve remission. After the first two weeks, a patient's AD treatment response should be evaluated to determine whether the treatment is adequate; and, if not, optimisation steps should be implemented (see section 2.3.2). If the treatment and AD dosage are deemed adequate, a patient needs eight to 10 weeks before a significant reduction in symptoms occurs (Bauer *et al.*, 2013). After the acute phase, an MDD patient should achieve full remission before an individual can be considered to be in the continuation phase. The aim of the continuation phase is to reduce the risk for relapse (Bauer *et al.*, 2013). The continuation phase is the first six to nine months after full remission was achieved. A continuation treatment period longer than nine months is recommended for patients who have a long history of MDD (Rush & Kupfer; 2001) and in patients who are still experiencing residual symptoms (Bauer *et al.*, 2013). Lastly, the maintenance treatment phase is also known as the prophylactic treatment phase and is designed to prevent a new depressive episode and ultimately suicide after full remission was achieved. According to Hirschfeld (1994), the maintenance treatment period can last for six to 24 months. A patient can consider treatment discontinuation if the individual did not experience any relapse during the maintenance phase. However, patients should be closely monitored during the discontinuation of AD treatment for the return of depressive symptomatology. With the faintest hint of returning symptoms during AD, tapering a patient should immediately be reinstated on AD treatment at the same dosage as during the maintenance phase and continue treatment for another six months before again attempting AD discontinuation (Bauer *et al.*, 2013).

#### **2.4.2 Treatment-resistant depression and tardive dysphoria**

MDD is characterised by recurring depressive episodes that can last for a short period of time (two to four weeks) or for extended periods of time (between seven and nine months) (Posternak *et al.*, 2006). Randomised controlled trials have revealed that maintenance AD treatment may lower the risk of relapse in the first year after an acute episode (Keller *et al.*, 1998; Reynolds *et al.*, 1999). However, although the recognised duration of treatment with an AD is nine to 12 months for an initial episode, longer for recurrent episodes and high risk patients (see section 2.3.1 above), numerous patients still experience recurrent depressive episodes despite being on chronic AD therapy (El-Mallakh *et al.*, 2011; Thase & Rush, 1995). When treatment still fails after the optimisation of AD treatment, such patients are considered to have treatment-resistant depression (TRD). Optimisation of AD therapy may include a single AD trial, two different monotherapy trials or more than one augmentation trial (Sackeim, 2001; Thase & Rush, 1995). The underlying cause of TRD is still undetermined and it seems that the prevalence might be on the rise. Whereas earlier estimates of TRD ranged between 15 and 20% of MDD patients (Burrows *et al.*, 1994), more recent work has found that almost 40% of MDD patients may have TRD (Keitner *et al.*, 2006; Shelton *et al.*, 2001; Thase & Rush, 1995). Several studies have proposed that inadequate dosing of AD drugs (Byrne & Rothschild, 1998; Hirschfeld *et al.*, 1997), or the development of tolerance, may contribute to the drastic increase in TRD. Tolerance to ADs occurs when a patient is in the maintenance phase of AD therapy and the depression symptoms return (Fava & Offidani, 2011). Some studies even suggest that chronic AD therapy itself may contribute to a chronic depressive syndrome (Fava, 2003; Sharma, 2006).

Tardive dysphoria can be defined as a chronic, frequently treatment-resistant depressive state with onset during on-going, persistent AD treatment (El-Mallakh *et al.*, 2011). At first, patients with recurrent MDD will experience a positive response to initial AD therapy, but on long-term treatment, the depressive state is perpetuated and can even worsen in some patients (El-Mallakh *et al.*, 2011). Between nine and 57% of MDD patients will experience a recurrent depressive episode (Pigott *et al.*,

2010) while on chronic AD therapy (Byrne & Rothschild, 1998). Only 30 to 60% of patients that experience relapse will respond positively to augmentation strategies, such as an increase in AD dosage (Schmidt *et al.*, 2002), change to another AD (Poirier & Boyer, 1999) or adding another AD (Blier *et al.*, 2010). In patients who have developed tardive dysphoria, on-going AD treatment may prolong TRD and ultimately cause chronic depression to become permanent (El-Mallakh *et al.*, 2011).

### **2.4.3 Antidepressant discontinuation syndrome**

Most classes of ADs are associated with discontinuation syndrome (Hosenbocus & Chahal, 2011), with the possible exception of agomelatine (de Bodinat *et al.*, 2010). It is especially prevalent with TCAs, SSRIs and SNRIs (Haddad & Anderson, 2007; Hosenbocus & Chahal, 2011; Narayan & Haddad, 2011). Because ADs are not linked to drug-seeking behaviour and addiction, the term 'discontinuation syndrome' is used rather than 'withdrawal syndrome' in order to prevent a false impression that AD treatment is addictive or can lead to drug dependence (Haddad & Anderson, 2007). Discontinuation syndrome occurs after the too rapid tapering or abrupt cessation of AD treatment, particularly if there is a significant reduction in the prescribed daily dosage (PDD) (Hosenbocus & Chahal, 2011). The symptoms of the SSRI discontinuation syndrome include flu-like symptoms such as headaches, nausea, light headedness, body aches, chills, paraesthesia, insomnia, anxiety and agitation (Gelenberg *et al.*, 2010). These symptoms are especially evident in ADs with a short half-life (Baldwin *et al.*, 2007), and resolve quickly after the SSRI is restarted (Haddad, 2001). Long half-life SSRIs, such as fluoxetine, seldom induce this syndrome (Price *et al.*, 2003; Tint *et al.*, 2008). The underlying neurobiology of these symptoms seems to involve perturbations (i.e. excess and/or deficits) in serotonergic transmission, as well as disruption in glutamate signalling. Much of the risk for ADs rests on the delicate balance between 5-HT<sub>1A</sub> and 5-HTT density, both of which are closely regulated by pathologically (i.e. depression) or pharmacologically (i.e. using an SRI) altered 5-HT levels. Moreover, limbic density and activity of monoamine oxidase (MAO) are also elevated in depression (Meyer *et al.*, 2006), which will also influence 5-HT<sub>1A</sub> and 5-HTT density via its protracted effects on 5-HT metabolism. More importantly, the latter anomaly persists into recovery after SSRI treatment (Meyer *et al.*, 2006), whereas a persistent deficit in monoamine neuromodulation may be a factor in recurrence. It has been suggested that ADS may also contribute to a worsening prognosis over time by activating specific sub-cellular pathways involved in neuroplasticity and adaptive responses to stress, response to AD treatment, and eventually negatively impacting recovery over the long term (Harvey *et al.*, 2003; Harvey *et al.*, 2003).

There are several reasons why patients suddenly stop taking their AD, which include non-compliance due to side effects, accidentally missing a dose, discontinuation following pregnancy, cost of treatment, and drug holidays, to mention only a few (Olver *et al.*, 1999). A retrospective study by Coupland and co-workers in a group of patients using SSRIs revealed that diagnoses, sex and age did not add to the risk for discontinuation syndrome (Coupland *et al.*, 1996). Antidepressant discontinuation syndrome incidence and severity seem to be more closely associated with higher dosages (Perahia *et al.*, 2005) and treatment periods longer than five weeks (Haddad, 1998; Rivas-Vazquez *et al.*, 1999). ADS is a neglected clinical phenomenon, often disregarded by clinicians and patients alike as just a transient adverse effect following AD discontinuation. However, it appears to have more insidious effects and sequelae. ADS is the focus of a review paper that forms part of the objectives of this study (Harvey & Slabbert, 2014).

### **2.4.4 Co-prescribing of GABAergic drugs in MDD**

The complex nature of MDD, particularly the variable presence of a number of symptoms as well as comorbid disorders related to sleep and anxiety often necessitates the need for co-prescribing of other

classes of psychotropic together with the AD (Huedo-Medina *et al.*, 2012). Moreover, side effects associated with some ADs, such as anxiety and insomnia with SSRI's, also often prompts co-prescribing (Edwards & Anderson, 1999).

Drugs acting on  $\gamma$ -amino-butyric acid (GABA) signalling, otherwise referred to as GABAergics (eg. benzodiazepines, zolpidem and zopiclone) are currently the most widely prescribed psychotropic drugs world-wide (Huedo-Medina *et al.*, 2012) The co-morbidity between anxiety disorders and depression is approximately 50 – 60% (Kaufman & Charney, 2000; Meijer *et al.*, 2004; Sanyal *et al.*, 2011) making the co-prescribing of ADs in combination with anxiolytics and sedative hypnotics fairly common (Valenstein *et al.*, 2004). Although there is the perception that such prescribing should benefit the treatment of MDD, clinical trials have found benzodiazepines have a limited effect on the treatment of MDD as they only address the agitation, insomnia and anxiety associated with MDD (Birkenhager *et al.*, 1995). However, benzodiazepines are closely associated with adverse effects such as dependence, discontinuation withdrawal and impaired cognition that ultimately limit their efficacy (Valenstein *et al.*, 2004). These clinical detractors have discouraged the use of benzodiazepines in the treatment of MDD, and as stipulated by international guidelines (American Psychiatric Association, 2010). The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Disorders (CANMAT) recommends the use SSRI and SNRI as the first-line treatments for anxiety associated with MDD (Kennedy *et al.*, 2009). Furthermore, the American Psychiatric Association (APA) recommends that the use of benzodiazepines should be limited and that benzodiazepine should not be used as a first-line option in the treatment anxiety especially in patients with severe MDD (American Psychiatric Association, 2010). Moreover, recent studies have suggested that  $\gamma$ -amino butyric acid (GABA) mimetic sedative hypnotics may be detrimental or counter-productive to AD treatment outcome. A pre-clinical study by Wu and Castren suggested that co-administration of diazepam with fluoxetine abrogates the effects of fluoxetine on crucial sub-cellular processes related to AD action (Wu & Castren, 2009). In the clinical scenario, chronic use of benzodiazepines has been found to aggravate depression and even increase the risk of suicide (Lader & Petursson, 1981; Ryan *et al.*, 1968). In contrast, benzodiazepines are suggested to be advantageous during the initial treatment phase (two to four weeks) of MDD as it has a faster onset of action and thus reduces anxiety related symptoms associated with both MDD and AD induced anxiogenic effects (Birkenhager *et al.*, 1995; Edwards & Anderson, 1999; Howard *et al.*, 2014; Outhoff, 2010). Importantly, benzodiazepines have been found to increase AD treatment compliance during the first weeks of treatment compared to patients taking ADs alone and to reduce dropout rates, but after six to twelve weeks benzodiazepines effects on AD treatment compliance diminished significantly (Furukawa *et al.*, 2001).

Within the benzodiazepine class there are differences in terms of potency, onset of action and half-life (Outhoff, 2010). Clonazepam and diazepam are proven to be as effective anxiolytics as alprazolam, the latter also being the only benzodiazepine that is claimed to have antidepressant-like effects (Bandelow *et al.*, 2008; Lesser *et al.*, 1988; Nutt, 2005). Lorazepam and other benzodiazepine associated with short a half-life (lormetazepam, oxazepam and temazepam) is not recommended as anxiolytics in MDD patients due to their increased risk for dependency (Davidson, 2010; Kennedy *et al.*, 2009).

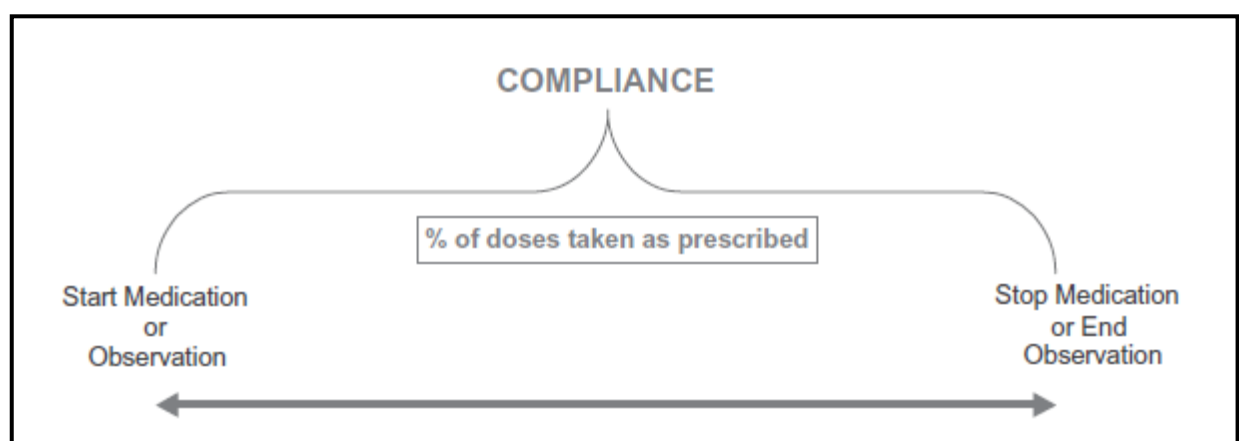
Another class of sedative hypnotics include the non-benzodiazepine group of GABAergic drugs such as zolpidem and zopiclone. Zolpidem and zopiclone is currently one of the most frequently dispensed sedative hypnotics (Huedo-Medina *et al.*, 2012) and are frequently co-prescribed with ADs for the treatment of insomnia associated with MDD (Valenstein *et al.*, 2004). However, overuse of these drugs

is associated with marked cognitive impairment and dementia, which could take up to six months to improve after the discontinuation of these drugs (Puustinen *et al.*, 2014).

## 2.4.5 Patient non-compliance

### 2.4.5.1 Compliance vs. adherence

In the literature, there is quite some controversy about the use of terms ‘compliance’ versus ‘adherence’ to describe how regularly a patient uses his or her prescribed medicine. In an article published in 2005 by Colom and co-workers, they referred to the term compliance as follows: “a patient must follow the advice of a medical practitioner without question” (Colom *et al.*, 2005). They recommended that the term adherence should be used as defined by the WHO: “the extent to which a person’s behaviour – taking medication, follow a diet, and/or executing a life style changes – corresponds with agreed recommendations from a healthcare provider” (WHO, 2003). However, in 2008, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work group developed a definition for compliance over a three-year period looking at different international reviews and discussions (Cramer *et al.*, 2008), and the following definition was proposed for compliance (synonym: adherence): “medication compliance refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking” (Cramer *et al.*, 2008). For the purpose of this thesis, the term compliance will be used as defined by ISPOR (see Figure 2.10).



**Figure 2.10:** Compliance is calculated over a period of time from the start of therapy until the end of the observation period and is expressed as a percentage (%) (Cramer *et al.*, 2008).

### 2.4.5.2 Non-compliance to antidepressant treatment

The term ‘non-compliance’ means much more than merely failing to take prescribed medicine. Non-compliance manifests in several ways, such as a patient taking only some of the prescribed medication, taking a lower dosage than prescribed, missing or skipping doses, delaying taking the prescribed AD(s), taking drug holidays, and patients who are fully compliant to their pharmacological treatment regimens, but fail to comply with other therapeutic interventions (Colom *et al.*, 2005; Demyttenaere *et al.*, 2001).

The management of MDD is severely compromised by non-compliance (Osterberg & Blaschke, 2005). Treatment of MDD is recommended to continue for at least four to six months from the time of

remission to prevent relapse (Keller *et al.*, 2002; NICE, 2009), which is extended in high-risk patients and/or those with a history of treatment resistance. Several studies have shown that the remission of MDD is higher in compliant than in non-compliant patients (Akerblad *et al.*, 2008; Akerblad *et al.*, 2006); and furthermore, that sustained AD use over 12 to 36 months may further decrease the risk of relapse by up to 70% compared to non-compliant patients (Geddes *et al.*, 2003). In a Spanish study, 56% of patients discontinued their AD treatment within the first four months, whereas only 22% maintained satisfactory adherence over the period of five years of the study (Serna *et al.*, 2010). Many studies concur that between 30 and 60% of patients do not comply with AD treatment (Cramer, 1995; Demyttenaere, 1997), that up to 30% of patients are likely to stop taking ADs within the first month after the start of treatment, and that 45 to 60% of patients will have stopped their prescribed treatment by the end of the third month (Hotopf *et al.*, 1997; Lin *et al.*, 1995; Robinson *et al.*, 1995). Without adequate treatment, patients will experience further relapses, depressive episodes and an increased risk for suicide (Frank *et al.*, 1992; Meehan *et al.*, 2006). Furthermore, preclinical studies demonstrated that inappropriate discontinuation might evoke a specific sequence of neurobiological events that underlie relapse and treatment resistance (Harvey, 2006; Harvey *et al.*, 2002; Harvey *et al.*, 2003). Therefore, compliance and persistence should be key concerns in the pharmacological management of MDD.

#### **2.4.5.3 Risk factors for non-compliance**

Patients with insufficient knowledge regarding their mental illness tend to have unfounded fears about prescribed AD treatment, such as fear of dependence, the stigma associated with the use of psychotropic drugs, seeing ADs as a danger to their physical health, and a negative state of mind about being controlled by a drug (Colom *et al.*, 2005; Morselli *et al.*, 2004). Patients with a history of substance abuse have an increased risk for non-compliance to AD treatment (Colom *et al.*, 2000). Furthermore, AD treatment-related factors such as adverse effects experienced while taking ADs (Weiss *et al.*, 1998) and higher number of drugs to be taken in combination regimens (Colom *et al.*, 2005) in the treatment of MDD can all contribute in AD non-compliance.

### **2.5 Depression and co-morbid diseases**

This section of the literature study will focus on the different ailments that are commonly co-morbid with MDD and the complications it introduces. For the most part, these co-morbid diseases need to be treated effectively in order to enhance the efficacy of AD treatment of MDD.

#### **2.5.1 Coronary artery disease and other cardiac disorders**

Coronary artery disease (CAD) is a common illness that is associated with a very high mortality rate (Lett *et al.*, 2004), and closely linked to psychiatric disorders (Rozanski *et al.*, 1999). MDD has been identified to be a major risk factor in the progression and onset of CAD (Musselman *et al.*, 1998) as well as other cardiovascular diseases (Van der Kooy *et al.*, 2007). Several studies have reported that patients who have suffered a myocardial infarction and who have MDD have an increased mortality rate compared to patients without MDD (Barth *et al.*, 2004; Carney *et al.*, 2004; de Jonge *et al.*, 2007; Glassman *et al.*, 2006). After an acute myocardial infarction, the lower survival rates seen in depressed patients may be partly due to decreased heart rate variability (HRV) (Carney *et al.*, 2005). In addition, there is also evidence suggesting that depressive symptomology associated with heart disease can be improved with the use of ADs (Ranga Rama Krishnan *et al.*, 2001; Thombs *et al.*, 2008). However, it is also important to note that other studies have had mixed results in attempting to relate cardiac-related mortality rates to AD use (Taylor *et al.*, 2005; van Melle *et al.*, 2007).

Several mechanisms, including platelet activity, HPA axis dysregulation, autonomic nervous system (ANS) and inflammation have been implicated in the correlation between MDD and cardiovascular diseases (Lett *et al.*, 2004). In both depressed and CAD patients, increased platelet reactivity has been observed (Kop *et al.*, 2002; Musselman *et al.*, 1996), which suggests the role of serotonin in MDD and platelet activity (Lett *et al.*, 2004). As mentioned before (section 2.1.3.2), HPA axis dysregulation is closely associated with the neurobiology of MDD and also plays a role in cardiovascular diseases by increasing risk factors such as increased blood pressure, hypercholesterolemia, obesity and raised heart rate (Rosmond & Bjorntorp, 2000). There is therefore a feasible relationship between MDD and cardiovascular illness. Furthermore, a study by Stein *et al.* (2000) demonstrated a correlation between MDD and impaired ANS functioning in a group of patients with CAD. This study found MDD patients to have a decreased heart rate variability (HRV) (this being an index of a healthy heart and good cardiac function with the ability to adapt both internal and external stressful demands) (Stein *et al.*, 2000). Another study found a correlation between reduced baroflex cardiac control (a measure of ANS activity) and depressive symptom severity in patients with CAD (Watkins & Grossman, 1999). Lastly, inflammation is closely associated with endothelial damage, which, in turn, contributes to atherosclerosis and atherothrombosis over a period of time and instigated by chronic stress (Halaris, 2013; Ross, 1999). A likely cause for the underlying stress is mental disorders of which MDE is one of the most prevalent, leading to sustained sympathetic overdrive and decreased vagal tone (Halaris, 2013). A constant decrease in vagal tone adds to the pro-inflammatory status, which affects the regulation of serotonergic neurotransmission. The increased release of certain pro-inflammatory and stress hormones (see previously discussed in section 2.1.3.2) by macrophages and microglia up-regulates the rate-limiting enzymes in the metabolic pathways of tryptophan. The result is a bypass in the metabolism of tryptophan away from serotonin formation to the kynurenine pathway that ultimately leads to the formation of the neurotoxic metabolites, 3-hydroxyanthranilic acid and quinolinic acid (Halaris, 2013).

The TCA class has been used successfully in the treatment of MDD in patients with ischemic heart disease (Nelson *et al.*, 1999), although care should be taken in patients with a medical history of prolonged QT intervals, subclinical sinus node dysfunction, ventricle arrhythmia and in patients who have suffered a recent myocardial infarction (Gelenberg *et al.*, 2010). ADs such as the SSRIs, SNRIs and bupropion seem to be safer to use in patients with a history of cardiac illness (Glassman *et al.*, 2002; Taylor *et al.*, 2005; Thombs *et al.*, 2008).

### **2.5.2 Stroke**

An estimated one third of patients who have suffered a stroke develop MDD during the first weeks to months after the incident, with a significant number of patients who will develop MDD (Hackett *et al.*, 2005; Paolucci *et al.*, 2006; Rovner & Casten, 2008). Some researchers suggest that patients must start AD treatment as soon as possible after a stroke in order to reduce rates of MDD (Andersen *et al.*, 1994). This practice may even decrease mortality (Jorge *et al.*, 2003), although results obtained from meta-analysis are varied (Chen *et al.*, 2007; Hackett *et al.*, 2005). The development of MDD after a stroke is associated with severe disability and an increase in mortality rates (House *et al.*, 2001; Paolucci *et al.*, 2006). The SSRIs are indicated in patients who have suffered a stroke because they are better tolerated and have fewer contraindications in already ill patients (Cole *et al.*, 2001; Swenson *et al.*, 2006). Extra care should be taken when stroke patients are on anticoagulant medication (warfarin) and antiplatelet (clopidogrel and aspirin), because of the increased bleeding risk (Ciraulo *et al.*, 2011; Holbrook *et al.*, 2005; Serebruany, 2006).

### 2.5.3 Obesity

Patients with a body mass index (BMI) higher than 40, and overweight women in particular, display an increased incidence of MDD (Fabricatore & Wadden, 2006). Furthermore, patients with binge eating disorder also have higher rates of developing MDD (Gelenberg *et al.*, 2010). Earlier, the importance of BDNF as an endogenous regulator of mood was described (see section 2.1.3.2). Interestingly, BDNF regulates appetite and energy metabolism, and is, in turn, suppressed by hyperphagia, obesity, hyperglycaemia, hyperinsulinaemia, hyperleptinaemia and insulin resistance (Duan *et al.*, 2003). Moreover, its production is increased by exercise (Duan *et al.*, 2003). Two other mechanisms have also been proposed to describe the relation between MDD and obesity. Firstly, the dysregulation of the HPA response and elevated cortisol levels suggests a neuroendocrine link between MDD and obesity (Lupien *et al.*, 2009). Chronically stressed patients have elevated cortisol levels, which have been found to promote weight gain (Ottoson *et al.*, 2000). Secondly, the inflammation response associated (see section 2.1.3.2) with MDD might be particularly pronounced in obese patients, as has been found in one study (Miller *et al.*, 2002). The mechanism underlying the relationship between MDD and obesity warrants further investigation, as the current literature regarding this matter is still very limited. Depression symptoms such as fatigue, lack of motivation and disrupted eating habits make exercising difficult, while weight gain associated with AD use further worsens the situation (Malone *et al.*, 2005; Zimmermann *et al.*, 2003). The TCAs and mirtazapine have the highest tendency for weight gain and while the SSRIs, MAOs and the SNRIs have a less pronounced effect (Zimmermann *et al.*, 2003), this is not always definitive (Harvey & Bouwer, 2000). Bupropion and agomelatine are good alternatives in the treatment of MDD in overweight and obese patients, because, in general, they are weight neutral. In fact, at the start of treatment, bupropion may even cause weight loss (Croft *et al.*, 2002; Jain *et al.*, 2002). It is important to closely monitor those patients whose weight tends to increase while on ADs, especially since weight gain may adversely affect compliance to AD treatment (Tamburrino *et al.*, 2009).

### 2.5.4 Type 2 diabetes mellitus

For some time now, the question has been asked: Is it MDD that causes type 2 diabetes mellitus (T2DM) or *vice versa*? This question has been studied closely in recent years, with researchers concluding that the relationship between MDD and T2DM is bi-directional (Mezuk *et al.*, 2008; O'Connor *et al.*, 2009). A recent meta-analysis by Mezuk and co-workers reported that the relative risk for T2DM in depressed patients is 1.60 (95% CI 1.37-1.88) and the relative risk for MDD in patients with pre-existing T2DM is 1.15 (95% CI 1.02-1.30) (Mezuk *et al.*, 2008). However, several meta-analyses could not establish a definite association between MDD and diabetes mellitus (Ali *et al.*, 2006; Bateman & Fonagy, 2008; Golden *et al.*, 2008). Nevertheless, MDD plays a significant role in a number of diabetes complications, such as nephropathy, neuropathy, macro-vascular complications, diabetic retinopathy and sexual dysfunction (de Groot *et al.*, 2001). One study suggests that compliance to diabetes treatment and diet regulations decreases during an MDD episode (Lustman & Clouse, 2005).

Although some authors have found a relationship between MDD and T2DM, little attention has been paid to describe the underlying biological pathways that link these disorders. This co-morbidity can be best explained by biological factors underlying stress and inflammation. The main characteristics of T2DM include insulin resistance and recurrent hyperglycaemia, where both these aspects of T2DM can lead to systemic inflammation (Stuart & Baune, 2012).

Brain-derived neurotrophic factor (see section 2.1.3.2) is another mechanism that has been investigated in recent years and that may play an important role in the pathology of both MDD and T2DM. In a

research report, Xu *et al.* (2003) suggested that increased levels of BDNF in the ventromedial hypothalamus may control food consumption and maintain an energy balance (Xu *et al.*, 2003). Furthermore, in obese and diabetic mice, BDNF treatment proved to be effective in significantly suppressing blood glucose, food consumption and dietary body weight gain, and increases the energy expenditure, lipid and glucose metabolism, as well as the activity of the sympathetic nervous system (Tsuchida *et al.*, 2001; Tsuchida *et al.*, 2002). These results have not yet been replicated in humans, but a study by Suwa and co-workers has found that increased levels of BDNF are associated with the prevalence of T2DM, and correlate with total and abdominal subcutaneous fat mass as well as energy metabolism in patients diagnosed with T2DM (Suwa *et al.*, 2006).

AD treatment may also affect glucose control, as some evidence suggests that TCAs might worsen glycaemic control in diabetes patients, whereas SSRIs may be preferable in diabetic patients with MDD (Ghaeli *et al.*, 2004; Lustman *et al.*, 1997). Furthermore, euglycemic agents, such as the glitazones, have antidepressant effects in animals (Kemp *et al.*, 2012:1172) and in humans (Kashani *et al.*, 2013:774).

## **2.6 Neuropsychiatric manifestations and disorders**

### **2.6.1 Anxiety disorders associated with MDD**

Anxiety disorders are the most common co-morbid psychiatric disorder associated with MDD (Zimmerman *et al.*, 2002). In an epidemiological study conducted in MDD patients, 62% of these patients met the criteria for generalised anxiety, 52% for social phobia, 50% for posttraumatic stress disorder (PTSD), 48% for panic disorder, 43% for specific phobia and 42% for obsessive-compulsive disorder (Kessler *et al.*, 2005). Therefore, the frequency of the co-morbidity between MDD and anxiety is relatively high, which leads to the question whether these disorders should be addressed as two separate disorders that frequently overlap each other or as different facets of the same underlying disorder (Tyrer, 1996). Several studies have demonstrated that anxiety disorders are a risk factor for developing MDD (Ball *et al.*, 1994 ; Wittchen *et al.*, 2000). The co-morbidity between MDD and anxiety holds a number of complications, such as difficulty diagnosing the primary disorder due to overlapping symptoms. Optimal treatment regimens to treat both conditions at the same time are still limited. This co-morbidity is also an indicator of a more severe psychiatric disorder and, lastly, patients suffering from both MDD and anxiety disorder have a four times higher incidence of suicidal ideation and suicide attempts when compared to patients only diagnosed with MDD (Fava *et al.*, 2004; Sareen *et al.*, 2005; Schoevers *et al.*, 2008).

The anxiety co-morbid with MDD can be effectively treated with ADs, with both the SSRIs and TCAs effective in this regard (Dunner, 2003). It is important to note that both these classes of ADs worsen anxiety and agitation symptoms at the start of treatment and it is therefore advised to start with small doses and gradually titrate upwards (NICE, 2009). Anxiolytic drugs such as the benzodiazepines can also be added during the initial phase of AD treatment. Because benzodiazepines do not have AD activity and due to their potential for abuse, they should not be used as monotherapy in the chronic treatment of anxiety in MDD patients (Gelenberg *et al.*, 2010).

### **2.6.2 Dysthymic disorder**

Dysthymic disorder is a chronic mood disorder, although not as severe as MDD. However, when both dysthymic disorder and MDD occur in a patient, the phenomenon is known as double depression (Keller

*et al.*, 1995). Double depression can be successfully treated with combination AD therapy and psychotherapy (Browne *et al.*, 2002).

### **2.6.3 Dementia**

Dementia patients are highly susceptible to developing MDD, but in many cases this is overlooked (Gelenberg *et al.*, 2010). ADs may be useful in the treatment of depressive symptoms in dementia patients, although they do not improve cognition. Studies in this regard are very limited (Bains *et al.*, 2002; Lyketsos *et al.*, 2003; Thompson *et al.*, 2007). ADs with anticholinergic effects, such as TCAs and some SSRIs, such as paroxetine, should be avoided in dementia patients, as they can adversely affect memory and attention span. ADs such as bupropion, fluoxetine, sertraline and trazodone are more advocated in these patients (Moore & O'Keefe, 1999), and possibly agomelatine (Harvey & Slabbert, 2014).

### **2.6.4 Personality disorder**

Patients with any form of personality disorder tend to be less responsive to AD treatment in terms of enduring MDD symptoms and social functioning, compared to depressed patients without a personality disorder (Newton-Howes *et al.*, 2006). In addition, if that patient is suffering from MDD, personality disorders delay time to remission and increase an individual's risk for a depressive episode (Grilo *et al.*, 2005). Personality disorders increase the risk for MDD and patients suffering from both disorders have a significantly higher incidence of attempting suicide compared to MDD patients without co-morbid personality disorder (Gunderson *et al.*, 2008; Vieta *et al.*, 1992).

## **2.7 Human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) and MDD**

In 2012, the UNAIDS World AIDS Day Report estimated that, at the time, approximately 34 million people worldwide were infected with the human immunodeficiency virus (HIV), whereas 69% of these infected patients live in sub-Saharan Africa (UNAIDS, 2012). In the United States, more than a million individuals are infected with the HIV virus, while approximately 50 000 contract HIV each year (Centers for Disease Control and Prevention, 2011). The prevalence for HIV/AIDS in South Africa is estimated at 17.3% in the age group of 15 to 49 years and approximately 5.6 million people in South Africa are living with HIV/AIDS. South Africa is one of the countries with the highest mortality rates in the world, with nearly 270 000 HIV/AIDS-related deaths in 2011 (WHO, 2011). However, combination antiretroviral therapy (cART) has been successful in improving morbidity and decreasing the mortality rate of HIV/AIDS (Bhaskaran *et al.*, 2008; Crum *et al.*, 2006; Lima *et al.*, 2009). Furthermore, cART can suppress HIV-1 RNA levels and increase CD4 T cell lymphocytes, but only if the cART is associated with excellent compliance and persistence (Bae *et al.*, 2011; de Bruin *et al.*, 2010).

The co-morbidity between chronic illnesses and MDD is a well-recognised phenomenon. Chronically ill patients display two to three times higher rates of MDD compared to healthy individuals of the same age and gender (Ali *et al.*, 2006; Schleifer & Macari-Hinson, 1989; Spijkerman *et al.*, 2005). Diabetes, asthma, epilepsy, cancer, coronary heart disease, hypertension and HIV/AIDS are among the most common chronic illnesses that are associated with an increased prevalence of MDD (Springer *et al.*, 2012). Looking at the symptomology of MDD, depressed patients tend to neglect themselves due to fatigue, low energy levels, impaired memory and a sense of helplessness (Katon, 2003). Patients with a chronic illness and co-morbid MDD have a significant decrease in compliance to self-care treatment

regimens (DiMatteo *et al.*, 2000), which may have a severe negative effect on the long-term treatment outcomes (e.g. reduced quality of life and daily functioning) (Plummer *et al.*, 2010; Singh *et al.*, 1999).

HIV-positive patients have double the incidence of MDD when compared to HIV-negative individuals (Ellis *et al.*, 2010; Lima *et al.*, 2007; Orlando *et al.*, 2002). There is also a definite association between late stage HIV (CD4 count of <200 cells/ $\mu$ L) and the incidence of MDD. Various studies have found a two and a half-fold increase in MDD in such patients (Alciati *et al.*, 2001; Ickovics *et al.*, 2001; Lyketsos *et al.*, 1996a; Lyketsos *et al.*, 1996b). A recent study by Lopes and co-workers found that HIV-positive men were more likely to have mood disorders (odds ratio = 6.10), major depressive disorder (odds ratio = 3.7), anxiety disorders (odds ratio = 4) and personality disorders (odds ratio = 2.5) when compared to HIV-negative males (Lopes *et al.*, 2012). Major depressive disorder is one of the main causes of psychiatric morbidity in HIV/AIDS patients (Kinyanda *et al.*, 2011). In a six-month follow-up study in South Africa, Olley and co-workers described a 34.9% prevalence for MDD at baseline, and a prevalence of 26% at follow-up among HIV/AIDS-infected patients (Olley *et al.*, 2006). However, elsewhere in the literature, there remains controversy about the prevalence of MDD in HIV/AIDS patients, broadly estimating the prevalence as between 3 and 54% (Cysique *et al.*, 2006; Gibbie *et al.*, 2007; Kinyanda *et al.*, 2011). Human immunodeficiency virus and acquired immunodeficiency syndrome are associated with neuropsychiatric complications caused by viral infection in the central nervous system, but also as a result of physiological changes caused by the progression of the illness as well as the treatment regimens (Pieper & Treisman, 2005). These physiological and psychiatric changes make it difficult to distinguish HIV/AIDS from MDD as they share many of the same symptoms (Elliott *et al.*, 2002; Hughes *et al.*, 2004), including cognitive impairment, sleep disturbances, loss of libido, impaired sexual functioning, appetite changes, anergia, lack of motivation and fatigue (Relf *et al.*, 2013). They may offer a feasible explanation for the large contrast in studies describing the prevalence of MDD in HIV/AIDS patients. One of the objectives of the current study is to provide an accurate reflection of the prevalence of MDD as a co-morbid illness with HIV/AIDS in the private health sector of South Africa.

A meta-analysis integrating data from 10 different studies in the United States of America found that patients infected with HIV/AIDS had almost double the frequency of MDD when compared to HIV-negative controls (Ciesla & Roberts, 2001; Relf *et al.*, 2013). Consistent with previous studies, that woman had a higher frequency of MDD than males, the same trend was identified in HIV-positive patients; women also have a higher prevalence of MDD when compared to HIV-positive males. In addition, two separate studies found that almost double the number of women with MDD and HIV/AIDS are likely to die from an HIV/AIDS-related cause when compared to HIV-positive women without MDD (Cook *et al.*, 2006; Ickovics *et al.*, 2001). Patients with both MDD and HIV/AIDS experience a drastic decline in the quality of life, reduction in treatment compliance, poor self-care, deteriorated treatment outcomes, social impairment, low occupational functioning and heightened social isolation (Chandler *et al.*, 2006; Rabkin, 2008). Furthermore, mortality rate is also increased, with HIV/AIDS-positive patients with MDD presenting with increased suicide rates and suicide ideation (Alciati *et al.*, 2001; Carrico *et al.*, 2006; Cooperman & Simoni, 2005; Haller & Miles, 2003). MDD associated with HIV/AIDS can nevertheless be effectively treated with the typical ADs such as TCAs, as well as SSRIs such as paroxetine and fluoxetine (Caballero & Nahata, 2005; Elliott *et al.*, 1998; Treisman *et al.*, 1994).

One of the essential elements for the successful treatment of HIV/AIDS is patient compliance to antiretroviral therapy (ART) (Angelino & Treisman, 2008; Treisman *et al.*, 2001). Patients who are HIV-positive must maintain a compliance rate of at least 95% in order to prevent virologic failure (Paterson *et al.*, 2000). Another problem associated with non-compliance to ART is the increased risk of viral

resistance, which ultimately leads to treatment failure (Chesney, 2006; Gonzalez *et al.*, 2011; Marcus, 2006; Schneider *et al.*, 2004). MDD in HIV-positive patients can be effectively treated with ADs, with several studies showing that SSRIs are better tolerated than TCAs in combination with antiretroviral treatment (Caballero & Nahata, 2005; Elliott *et al.*, 1998). What is uncertain is the impact of MDD on compliance to AD treatment in HIV/AIDS patients, and forms an important component to the current study.

## **2.8 Synopsis**

Major depressive disorder is a common mental disorder with an exceptionally high prevalence. The illness causes a great deal of suffering and drastically affects a person's ability to live a normal life. Although some relief is provided by the current treatment regimens, the majority of patients remain untreated or ineffectively treated. The onset of MDD usually starts in the early 20s, but affects patients of all ages from young children to elderly people.

MDD is a mental illness marked by functional and structural brain changes and molecular changes, and is determined by an environmental as well as a genetic component that further complicates its progression. The exact cause of MDD remains unknown and there is much on-going research aimed at identifying the illusive neurobiological target/s responsible for the illness, as well as searching and designing new generation ADs with improved efficacy in treating the illness.

Non-compliance to AD treatment remains one of the major hurdles in effectively treating MDD. Although there are several classes of ADs on the market, their efficacy remains modest due to inadequately addressing the root biological cause of the illness, as well as the side effects of AD treatment and patients' perceptions regarding psychotropic drugs.

Finally, the diagnoses and treatment of MDD are further complicated because of its association with several co-morbid diseases, such cardiovascular disorders, obesity, type 2 diabetes mellitus, anxiety disorders, dysthymic disorders, dementia personality disorders and HIV/AIDS.

## CHAPTER 3: MANUSCRIPT 3.1

In this chapter, a manuscript titled

“New insights on the antidepressant discontinuation syndrome” is presented. The paper was submitted to **Human Psychopharmacology: Clinical and Experimental** as a review article, and prepared according to the specific *Instructions to the Author* for this journal (provided in Addendum A). The references for this manuscript are provided at the end of this chapter.

This manuscript has been accepted and published online

Instructions to the author can be viewed with the following link:

[http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1099-1077/homepage/ForAuthors.html](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1099-1077/homepage/ForAuthors.html) Date of access: 6 Oct. 2013.

### 3.1 Article 1

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REVIEW ARTICLE

## New insights on the antidepressant discontinuation syndrome

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**Objective** Antidepressants are at best 50–55% effective. Non-compliance and the antidepressant discontinuation syndrome (ADS) are causally related yet poorly appreciated. While ADS is associated with most antidepressants, agomelatine seems to be devoid of such risk. We review the neurobiology and clinical consequences of antidepressant non-compliance and the ADS. Agomelatine is presented as a counterpoint to learn more on how ADS risk is determined by pharmacokinetics and pharmacology.

**Design** The relevant literature is reviewed through a MEDLINE search via PubMed, focusing on agomelatine and clinical and preclinical research on ADS.

**Results** Altered serotonergic dysfunction appears central to ADS so that how an antidepressant targets serotonin will determine its relative risk for inducing ADS and thereby affect later treatment outcome. Low ADS risk with agomelatine versus other antidepressants can be ascribed to its unique pharmacokinetic characteristics as well as its distinctive actions on serotonin, including melatonergic, monoaminergic and glutamatergic-nitric systems.

**Conclusions** This review raises awareness of the long-term negative aspects of non-compliance and inappropriate antidepressant discontinuation, and suggests possible approaches to “design-out” a risk for ADS. It reveals intuitive and rational ideas for antidepressant drug design, and provides new thoughts on antidepressant pharmacology, ADS risk and how these affect long-term outcome. Copyright © 2014 John Wiley & Sons, Ltd.

**KEY WORDS**—half-life; anhedonia; anxiety; serotonin transporter; phasic receptor occupancy; neuroplasticity

### ANTIDEPRESSANT NON-COMPLIANCE: A MAJOR ADVERSARY TO SUCCESSFUL OUTCOME

In the treatment of depression, drug non-compliance is a long-standing problem (Keller and Boland, 1998). Several studies suggest that up to 30% of patients stop taking their antidepressant within the first month of initiating treatment and that 45–60% of patients stop taking their antidepressant by the end of the third month (Hotopf *et al.*, 1997). Several studies have demonstrated that antidepressant discontinuation is associated with an increased morbidity and mortality (Åkerblad *et al.*, 2008). The reasons for premature antidepressant discontinuation are various, including the stigma associated with mental illness, patients who feel better and under their own volition discontinue their

medication, and the occurrence of side effects. Indeed, sexual dysfunction (Sommer *et al.*, 2003), weight gain, nervousness (Goodman, 2004), disturbed sleep rhythms (Wilson and Mottram, 2004) and nausea (Sommer *et al.*, 2003) are troubling side effects that severely compromise compliance.

Interruption of antidepressant medication may lead to a complex physiological and neuropsychiatric syndrome referred to as an antidepressant “discontinuation reaction” (Wamer *et al.*, 2006; Narayan and Haddad, 2010), so named to prevent confusion with “withdrawal reaction” encountered with drugs of abuse. Antidepressant discontinuation syndrome (ADS) is most often (but not exclusively) associated with tricyclic antidepressants (TCAs), serotonin (5-HT) reuptake inhibitors (SRIs) and dual 5-HT noradrenaline (NA) reuptake inhibitors (SNRIs) (Haddad and Anderson, 2007; Narayan and Haddad, 2010). Approximately 20% of patients are affected by ADS following inappropriate and/or sudden discontinuation of their medication or at the start of medication tapering (Warner *et al.*, 2006). Although

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ADS is typically associated with dizziness, nausea, headache, lethargy, low mood, insomnia, tinnitus and imbalance (Table 1; Warner *et al.*, 2006; Narayan and Haddad, 2010; Clewes, 2012), the severity of discontinuation reactions varies between individuals and across a spectrum, with some patients manifesting an isolated symptom and others a cluster of symptoms (Haddad, 2001). Furthermore, ADS can be relatively short lived or last for months (Price *et al.*, 1996), the latter with serious ramifications for the patient. The reason for the large variation in duration and severity of ADS requires further study, although very likely has a biological basis that is dependent on the "illness state" of a particular patient and the specific pharmacological profile of the drug and its neurobiological targets, viz. 5-HT, acetylcholine (ACh), and NA. This together with how long the antidepressant has been administered prior to discontinuation and the ensuing effects on receptor state and sensitivity (that may differ over time in different brain regions), will influence the presenting symptoms of ADS as well as their long-term sequelae. Another contributor to the variation in ADS is individual differences in drug metabolism. Certain antidepressants are highly dependent on cytochrome P450 (CYP450) for their elimination from the body, while various ethnic populations display either rapid or slow CYP450-directed metabolism. Rapid metabolizers will quickly eliminate antidepressant from the body resulting in a sudden and drastic diminution of drug levels that will trigger a more severe ADS. A typical example is paroxetine that not

only has a short half-life ( $T_{1/2}$ ; see later) but is also a substrate for CYP450D6 as well as a potent inhibitor of this enzyme (Harvey, 1997). Paroxetine discontinuation in a rapid metaboliser will therefore disinhibit its own metabolism resulting in ADS that may be more severe than that experienced normally by slow metabolisers.

Antidepressant discontinuation syndrome can be as high as 46% in patients assessed 1 week after stopping an SRI or SNRI (Tint *et al.*, 2008). ADS is generally regarded as self-limiting with relatively benign somatic manifestations (Table 1) brought about by sudden changes in synaptic neurotransmitter levels following antidepressant withdrawal. Important to note is that ADS is distinct from relapse or a new depressive episode (Zajacka *et al.*, 2002), although there are a number of overlapping neuropsychiatric symptoms (see Table 1). However, symptoms that are more specific for ADS are especially somatic in nature such as influenza-like symptoms, nausea, imbalance, sensory manifestations and a host of other presentations depicted in Table 1. Although sleep disturbances such as insomnia and hypersomnia are common in depression, nightmares and excessive dreaming may be a product of excessive serotonergic activity that, as will be described shortly, may be a product of hyperserotonergia and hence more suggestive of the ADS. However, despite it being considered benign, ADS is nevertheless associated with significant discomfort and decreased quality of life, and, in rare occasions, may require hospitalization (Warner *et al.*, 2006). Moreover, misdiagnosis of ADS

Table 1. Summary of the somatic and psychiatric symptoms of antidepressant discontinuation syndrome versus depression relapse

Discontinuation		Relapse	
Somatic <sup>ab</sup>	Psychiatric <sup>c</sup>	Somatic <sup>d</sup>	Psychiatric <sup>d</sup>
<ul style="list-style-type: none"> <li>• Flu-like symptoms</li> <li>• Insomnia</li> <li>• Nausea</li> <li>• Dizziness</li> <li>• Lethargy</li> <li>• Headache</li> <li>• Imbalance</li> <li>• Sensory disturbances</li> <li>• Dysesthesias</li> <li>• Paresthesias</li> <li>• Bradykinesia</li> <li>• Akathisia</li> <li>• Temperature intolerance</li> <li>• Flushing</li> <li>• Diaphoresis</li> <li>• Tremors</li> <li>• Tinnitus</li> </ul>	<ul style="list-style-type: none"> <li>• Impaired cognition</li> <li>• Activation</li> <li>• Mania</li> <li>• Sleep disturbances</li> <li>• Irritability</li> <li>• Anxiety/agitation</li> <li>• Low mood</li> <li>• Tearfulness</li> <li>• Nightmares</li> <li>• Excessive dreaming</li> <li>• Suicidal ideation</li> <li>• Confusion</li> <li>• Psychosis</li> </ul>	<ul style="list-style-type: none"> <li>• Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month)</li> <li>• Decrease or increase in appetite nearly every day</li> <li>• Insomnia or hypersomnia nearly every day</li> <li>• Fatigue or loss of energy nearly every day</li> </ul>	<ul style="list-style-type: none"> <li>• Depressed mood</li> <li>• Markedly diminished interest or pleasure in all or almost all activities</li> <li>• Psychomotor agitation or retardation</li> <li>• Feelings of worthlessness or excessive or inappropriate guilt</li> <li>• Diminished ability to think or concentrate, or indecisiveness</li> <li>• Recurrent thoughts of death</li> </ul>

<sup>a</sup>Federal Bureau of Prisons. Management of Major Depressive Disorder Federal Bureau of Prisons Clinical Practice Guidelines, August 2009.

<sup>b</sup>Clewes (2012).

<sup>c</sup>Haddad and Anderson (2007).

<sup>d</sup>American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC.

may lead to harmful medical and drug interactions, as well as unnecessary medical admissions and investigations (Haddad, 2001; e.g. see Clewes, 2012). Furthermore, rarely ADS may lead to severe psychiatric presentations including hypomania, mania and delirium (Haddad and Anderson, 2007; Gahr *et al.*, 2013). In fact, the clinical impact can be severe in unipolar depressed patients when a clinician mistakes symptoms of hypomania or mania after antidepressant discontinuation and subsequently initiates treatment for bipolar depression, which might include long-term antipsychotic and mood stabilizing drugs (Narayan and Haddad, 2010). Importantly, when antidepressants are switched, ADS from the antidepressant that has been stopped may be misdiagnosed as an adverse side effect of the newly initiated antidepressant (Zajacka *et al.*, 1997), as has been described by Haddad and Qureshi (2000). This adverse response may alter the clinician's and the patient's perception of the replacement treatment. Thus, some patients might be unwilling to use psychotropic medication after experiencing ADS and thereby increase their vulnerability for future relapses of depression or anxiety disorders (Wamer *et al.*, 2006). Furthermore, because of the complex neurobiological response set in motion by the ADS (see later), this may adversely affect treatment response to the newly instated antidepressant. Indeed, earlier work has suggested that repeated non-compliance and antidepressant discontinuation may promote neurobiological mechanisms that predict relapse and treatment resistance, thereby adversely affecting long-term outcome (Harvey *et al.*, 2003). Altered glutamatergic and other neuro-damaging events, as will be discussed shortly, have been posited to be central to relapse in both depression (Harvey *et al.*, 2003) and schizophrenia (Emsley *et al.*, 2013). In this regard, MacQueen *et al.* (2003) have noted an association between more severe structural brain changes and starting and stopping antidepressant treatment. Over the long term, ADS can reduce the time between depressive episodes and significantly increase the risk of new episodes (Baldessarini *et al.*, 2010). Patients discontinuing their antidepressant have a 2.3 times higher risk of recurrence, while the time to the next recurrent depressive episode is one-third shorter versus compliant individuals (Viguera *et al.*, 1998; Baldessarini *et al.*, 2010).

Although there is no concrete evidence to suggest that the length of SRI treatment is linked to the development of higher frequency or severity of ADS symptoms (Baldwin *et al.*, 2007), ADS is uncommon in patients treated for less than 5–8 weeks, while higher dosages also tend to be associated with a higher incidence and greater severity of discontinuation symptoms (Hosenbocus and Chahal,

2011). This association with dose and duration of treatment suggests that ADS involves time-dependent neuroplastic events, not unlike that observed when an antidepressant is started up until the onset of therapeutic effects some weeks later (see Manji *et al.*, 2001; Popoli *et al.*, 2002; Krishnan and Nestler, 2008, for review), and which will be touched on later in this review. Generic substitution has also been purported to constitute a risk factor for ADS, reportedly because of an allowed 20% deviation in the formulation of the original drug (Wamer *et al.*, 2006).

Although ADS can be alleviated by immediately reinstating the original antidepressant or one with a similar mechanism of action (Tint *et al.*, 2007), prevention remains the most important treatment. Protocols aimed at improving adherence such as Web-based intervention strategies, especially those that are combined with coach support, are valuable and have delivered promising results (Mohr *et al.*, 2013). More amenable approaches include tapering after successful treatment and tapering with antidepressant switching (see British Medical Association and Royal Pharmaceutical Society of Great Britain, 2007; National Institute for Health and Clinical Excellence, 2011, for guidelines). Although no controlled data are available to recommend the effectiveness of tapering, time duration of tapering and the minimum dosage needed before ending antidepressant treatment (Tint *et al.*, 2007), it has been suggested that antidepressants administered for 8 weeks and longer should be tapered over a period of 4 weeks, although some advocate a more cautious approach (Haddad and Anderson, 2007). The bottom line here is that illness risk is *worsened* following rapid versus gradual discontinuation (Baldessarini *et al.*, 2010). Consequently, if treatment is stopped after successful treatment of depression and if there is no intention to switch, a wise choice would be not to limit the duration of the taper (Haddad and Anderson, 2007). When tapering with the goal of switching antidepressant treatment because of a lack of efficacy, tapering the first drug for longer than 14 days is impractical, as it will cause excessive delay before starting the new drug (Tint *et al.*, 2007). Start-taper switch, which refers to starting the new antidepressant while simultaneously tapering the previous drug, or abrupt switch is preferable when there are no potential interactions and no washout period is needed. The choice of switch also depends on the likelihood of discontinuation symptoms (see later) and the similarity between the two antidepressants (Tint *et al.*, 2007). Patients with a history of severe ADS, previous adverse experience regarding side effects and efficacy, or a history of non-compliance should also be taken into

account (Haddad and Anderson, 2007). Although earlier work has hinted at the possible negative effect of non-compliance and repeated discontinuation on long-term outcome (Harvey *et al.*, 2003), there remains an urgent need for studies to examine the association of a discontinuation syndrome with long-term outcome of depression. While there is merit in discussing the aspects of ADS prevention and/or its long-term implications, this review will focus on understanding its neurobiology at a more fundamental level.

#### NEUROBIOLOGICAL BASIS OF ANTIDEPRESSANT DISCONTINUATION SYNDROME

The pharmacological and pharmacokinetic profile of the prescribed antidepressant is a reliable predictor of ADS risk. For most, ADS symptoms are more common after the sudden discontinuation of antidepressants (Baldwin *et al.*, 2007), especially SRIs, for example paroxetine and sertraline (Thompson, 1998), and SNRIs, for example venlafaxine (Agelink *et al.*, 1997) and duloxetine (Warner *et al.*, 2006), but also atypical agents such as mirtazapine (Berigan, 2001) and trazodone (Peabody, 1987). Clinical experience strongly suggests that a short  $T_{1/2}$  provides added risk (e.g. paroxetine; Table 2). Because of the presence of its active metabolite, norfluoxetine, fluoxetine has an effective plasma  $T_{1/2}$  of up to 7 days (Harvey, 1997) and is widely recognized as being the SRI with the lowest incidence of ADS (Tint *et al.*, 2007; Table 2). In fact, fluoxetine is often used as rescue treatment in ADS induced by other SRIs. Nevertheless, the relationship between short versus long  $T_{1/2}$  may not be an absolute predictor of ADS. Price and co-workers (1996) reported that withdrawal reactions were 10 times higher in patients taking paroxetine when compared with patients taking fluvoxamine, despite both SRIs having similar half-lives (Table 2). Indeed, we have earlier noted that the CYP450 inhibitory potential of the agent is also a strong contributor

towards the risk of post-withdrawal ADS, for example paroxetine (Harvey, 1997). Moreover, neuro-receptor affinity of the drug in question also plays a prominent role in ADS risk, with antidepressants that acutely increase 5-HT (e.g. SRIs and SNRIs) and/or that interact with muscarinic ACh receptors (e.g. TCAs and paroxetine) having the greatest risk. In fact, despite a common site of action at the 5-HT transporter (SERT), SRIs are all structurally dissimilar with different receptor affinities (Harvey, 1997) and should be considered on individual merit and not as a class. Thus, paroxetine displays significant affinity for muscarinic cholinergic receptors (Harvey, 1997; Owens *et al.*, 2001) as well as the NA transporter (Tatsumi *et al.*, 1997), citalopram has notable affinity for histamine  $H_1$  receptors (Harvey, 1997; Harvey and Bouwer, 2000), sertraline also inhibits dopamine (DA) reuptake (Harvey, 1997), while fluoxetine is also a 5-HT $\alpha_2$  receptor antagonist (Sánchez and Hyttel, 1999). It is likely that variable affinities for these receptors play an important role in predicting the risk of ADS.

Chronic psychosocial and environmental stressors play a major role in the development of depression (Kendler *et al.*, 2001a, 2001b), with genetic variability determining the susceptibility of the individual to developing an anxiety or mood disorder and aiding in its recovery (Harvey, 2008). In the aftermath to stress, subsequent disabling of the circadian clock, the hypothalamic-pituitary-adrenal (HPA) axis, and disruption of inhibitory-excitatory  $\gamma$ -amino butyric acid (GABA)-glutamate signalling with deficits in neurotrophin release, such as brain-derived neurotrophic factor, culminate in structural changes in critical brain regions regulating the stress response, for example hippocampus (see Harvey *et al.*, 2003; Krishnan and Nestler, 2008; Savitz and Drevets, 2009; Renoir *et al.*, 2012). These diverse and interlinked cascades eventually culminate in disorganized biorhythms and depleted brain monoamines (5-HT, NA and DA), which are suggested to underlie the behavioural and cognitive deficits typical of depression. That ADS is more often seen following prolonged antidepressant treatment and in patients treated with higher dosages (Hosenbocus and Chahal, 2011) suggests that like antidepressant initiation (see Manji *et al.*, 2001; Popoli *et al.*, 2002; Krishnan and Nestler, 2008, for review), repeated non-compliance and ADS set in motion various time-dependent neuroplastic changes. Indeed, patients that have discontinued paroxetine during the maintenance phase of treatment for depression demonstrate a neuroendocrine stress response (Michelson *et al.*, 2000), while antidepressant discontinuation is associated with distinct functional changes in the brain (e.g. Henry *et al.*, 2003; Kaufman *et al.*, 2003).

Table 2. Half-life ( $T_{1/2}$ ) of selected antidepressants

Drug	Half-lives (hours)
Agomelatine	2.5
Duloxetine	11–16
Fluoxetine	96–216
Mirtazapine	20–40
Paroxetine	16
Sertraline	26
Fluvoxamine	15
Trazodone	7.1
Venlafaxine	3–13
Tricyclic antidepressants	24–36

Harvey (1997), Dolder *et al.* (2008) and De Bodinat *et al.* (2010).

That ADS mounts a bio-behavioural stress response suggests that long-term detrimental effects may ensue that will compromise outcome, especially by introducing an additional risk factor into an already vulnerable individual, with the associated risk for relapse and recurrence (Harvey *et al.*, 2003). Although depression is a multi-transmitter illness, current consensus has placed especially the 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors at the centre of antidepressant response (Blier, 2003; Millan, 2006), with the 5-HT<sub>2C</sub> receptor playing a central role in bio-behavioural stress responses (Martin *et al.*, 2014). Hence, their role in ADS may be equally as important.

Our current understanding of ADS is extremely limited, mainly because of the paucity of preclinical tools with which to model ADS. Moreover, behavioural data may be complicated by the highly subjective nature of the symptoms of ADS in humans (Blier and Tremblay, 2006; Heitzman and Solak, 2009), thus complicating the development of a suitable animal model. Nevertheless, neurochemical studies using antidepressant discontinuation protocols can provide important information relating to the molecular underpinnings of the syndrome. Although various animal protocols have been used to date, these invariably have not been applied to valid translational animal models, for example the Flinders Sensitive Line rat (Overstreet and Wegener, 2013). In fact, something that is essential to understanding ADS is to design an animal model where an antidepressant discontinuation protocol is applied to such a translational model (Harvey and Shahid, 2012). Nevertheless, some of the available non-translational studies are useful, and focus on the effects of abrupt SRI discontinuation and the effects after the washout period. What is especially interesting and relevant is that sudden antidepressant discontinuation after long-term treatment in animals has been found to evoke a behavioural stress response (Harvey *et al.*, 2002; Harvey *et al.*, 2006), thus not unlike that observed in humans who are suddenly withdrawn from their antidepressant (Michelson *et al.*, 2000).

Bjork and co-workers (1998) observed a significant increase in locomotor activity in rats following chronic fluoxetine treatment and abrupt discontinuation. The increase in locomotor activity suggests a withdrawal phenomenon that is not unlike the agitation and anxiety experienced in patient with ADS (Table 1). Similarly, rats chronically treated with citalopram for 2 weeks, or following citalopram discontinuation for 48 h, displayed an exaggerated acoustic startle response, also a surrogate marker of anxiety-like behaviour (Bosker *et al.*, 2010). Interestingly, these authors also found that 5-HT turnover (the ratio of 5-hydroxy indole acetic acid vs 5-HT) increased after the 48-h washout period following the chronic treatment period,

while chronic treatment did not affect the 5-HT turnover (Bosker *et al.*, 2010). Some authors have proposed that ADS symptoms such as anxiety, low mood and tearfulness (Table 1), as well as negative mood states (see Lane, 2014), reflect an adverse effect of the SRI on the DA reward system (Gardier *et al.*, 1994; Renoir, 2013). These limited studies concur that antidepressant discontinuation has distinct behavioural effects on levels of anxiety and locomotion, as well as involve perturbations in serotonergic and possibly dopaminergic function. Evidence for adaptive changes in 5-HT<sub>1A/1B</sub> autoreceptors known to be critically involved in the mechanistic actions of antidepressants is lacking (Renoir, 2013). However, as noted earlier, other signalling pathways are also implicated in ADS. For example, a hyperadrenergic drive may also explain some symptoms of ADS, while changes in noradrenergic activity in turn may adversely influence serotonergic pathways (Millan, 2003; Blier and Tremblay, 2006). Cholinergic overdrive was first noted following withdrawal of TCAs and SRIs (e.g. paroxetine) with strong antimuscarinic properties (Harvey, 1997), and is therefore also implicated in ADS (Blier and Tremblay, 2006). The latter is especially important considering the hypercholinergic hypothesis of depression (Jaffe *et al.*, 2013) so that excessive cholinergic drive during ADS may trigger relapse.

Earlier, we have suggested that ADS involves a state of hyperglutamergergia (Harvey *et al.*, 2002; Harvey *et al.*, 2003). Preclinical and clinical studies have established an increase in glutamatergic transmission following stress and as a core component of depression as well (Harvey, 2008; Wegener *et al.*, 2010; Gao and Bao, 2011). Considering that 5-HT can abrogate glutamate pyramidal neurons in the rat cortex (El Mansari and Blier, 1997), and that SRI discontinuation promotes a stress response in rats (Harvey *et al.*, 2002) and in humans (Michelson *et al.*, 2000), SRI discontinuation may very likely increase glutamate release (Karreman and Moghaddam, 1996; Timmerman *et al.*, 1999) as part of a stress response with subsequent effects on neuroplasticity and cell survival. Given the important role of the glutamate-nitric oxide (NO) system in neuroplasticity and depression (Esplugues, 2002; Harvey *et al.*, 2003; Dhir and Kulkarni, 2011; Wegener *et al.*, 2010), increased glutamate-NO signalling will eventually drive structural brain changes over time, as noted in the hippocampus of patients with a history of prolonged depression and repeated depressive episodes (Krishnan and Nestler, 2008; Savitz and Drevets, 2009). These neuroplastic changes emphasize the progressive nature of on-going stress on repeated depressive episodes if not aggressively treated or if antidepressant treatment is

not closely adhered to from the start (MacQueen *et al.*, 2003). Various classes of antidepressant inhibit NO synthase (NOS; Wegener *et al.*, 2003), while antidepressant discontinuation in animal models is associated with increased NO signalling (Tagliaferro *et al.*, 2001; Harvey *et al.*, 2006). Moreover, antidepressant discontinuation associated increase in NOS activity is reversed by a 5-HT<sub>1A/2C</sub> receptor antagonist (Harvey *et al.*, 2006), thereby emphasizing how altered 5-HT and 5-HT<sub>2C</sub> receptors especially are involved in activating neurotoxic/neuroplastic pathways following ADS. Interestingly, hyperserotonergia is also known to adversely affect neuroplastic changes associated with stress and as such will negatively affect resilience and long-term recovery (Vaidya *et al.*, 1999).

#### ANTIDEPRESSANT DISCONTINUATION SYNDROME: AN INSEPARABLE LINK WITH SEROTONIN?

As highlighted earlier, there are a number of possible role players in the neurobiology of ADS, yet 5-HT seems to play a dominant and/or regulatory part in many of these mechanisms. Indeed, recent evidence indicates that the C (-1019)G polymorphism of the 5-HT<sub>1A</sub> receptor gene may be implicated in paroxetine associated ADS (Murata *et al.*, 2010). This not only confirms a central role for 5-HT in ADS but also that genetic drug interactions play an important role in the development of ADS. As described in Table 1, ADS represents a complex and unpredictable neuronal response. Viewing these symptoms, and considering the earlier-described animal studies, it seems reasonable to suggest that the underlying neurobiology involves perturbations (*i.e.* excess and/or deficits) in serotonergic transmission, as well as a variable involvement of adrenergic, glutamatergic, dopaminergic, cholinergic and other pathways. However, much of the risk for ADS rests on the delicate balance between 5-HT<sub>1A</sub> and SERT density and/or sensitivity, both of which are closely regulated by pathologically (*i.e.* depressive condition) or pharmacologically (*i.e.* using an SRI) altered 5-HT levels (see Harvey *et al.*, 2003, for review). Altered serotonergic function in turn can modulate other neurotransmitter systems, particularly DA, NA and glutamate (as will be discussed later and in Figure 2). Moreover, limbic density and activity of monoamine oxidase (MAO) are also elevated in depression (Meyer *et al.*, 2006), which will also indirectly influence 5-HT<sub>1A</sub> and SERT density via its protracted effects on 5-HT metabolism. More important, the latter anomaly persists into recovery after SRI treatment (Meyer *et al.*, 2009), while a persistent deficit in monoamine neuromodulation may contribute to recurrence.

The 5-HT<sub>1A</sub> agonist, buspirone, can exacerbate ADS (Carrazana *et al.*, 2001). Although definitive conclusions are difficult, given the dualist properties of this drug and the uncertainty as to whether it is targeting presynaptic or postsynaptic 5-HT<sub>1A</sub> receptors, it does suggest that ADS presents with elements of *hyperserotonergia*. Considering the range of serotonergic manifestations evident in ADS, especially those of a neuropsychiatric nature such as anxiety, irritability and sleep disturbances (Table 1; Coupland *et al.*, 1996), postsynaptic 5-HT<sub>1A/2C</sub> receptors are very likely one of the central receptor systems responsible for ADS. Somatodendritic 5-HT<sub>1A</sub> receptors are down-regulated following chronic antidepressant use and are central to successful remission of the illness (Taylor, 2007; Stahl, 2013). Following abrupt discontinuation of the antidepressant, the ensuing decrease in presynaptic 5-HT concentrations in the vicinity of the cell body (Figure 1), and the down-regulated state of 5-HT<sub>1A</sub> autoreceptors, will evoke a disinhibition of 5-HT release and a relative increase in 5-HT release in distal projection regions of the 5-HT neuron (Figure 1), including activation of postsynaptic 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors, which will drive circadian rhythm disturbances and other neuropsychiatric changes leading to the typical symptoms of ADS (Table 1). This action can be expected from agents that acutely increase 5-HT release leading to a later down-regulation of 5-HT<sub>1A</sub> receptors, particularly SRIs and SNRIs, but also agents such as mirtazepine that also acutely increase 5-HT following inhibition of the  $\alpha_2$ -adrenoceptor (de Boer *et al.*, 1996). Unfortunately, no studies are available on the action of the latter agents on 5-HT<sub>1A</sub> and SERT expression and function, but because of their action on 5-HT release, a similar phenomenon is predicted.

On the other hand, *reduced* activation of postsynaptic 5-HT receptors (*or hyposerotonergia*) may also account for the manifestation of ADS (Figure 1; Blier and Tremblay, 2006). This has important validity in explaining why ADS is immediately attenuated with the reintroduction of an SRI. Indeed, Benmansour and co-workers (1999) have noted that down-regulation of SERT by an SRI will increase synaptic levels of 5-HT in the brain. In rats, SERT down-regulation following sertraline treatment appears to return to normal 1 week after cessation of treatment, while 5-HT<sub>1A</sub> autoreceptors remain desensitized for 48 h following antidepressant discontinuation (Blier and De Montigny, 1987), with mRNA levels for 5-HT<sub>1B</sub> receptors returning to normal after 3 days (Blier and Tremblay, 2006). Therefore, gradual recovery of SERT activity following SRI discontinuation plays a dominant role in the decrease in synaptic availability of 5-HT so that altered 5-HT<sub>1A/B</sub>

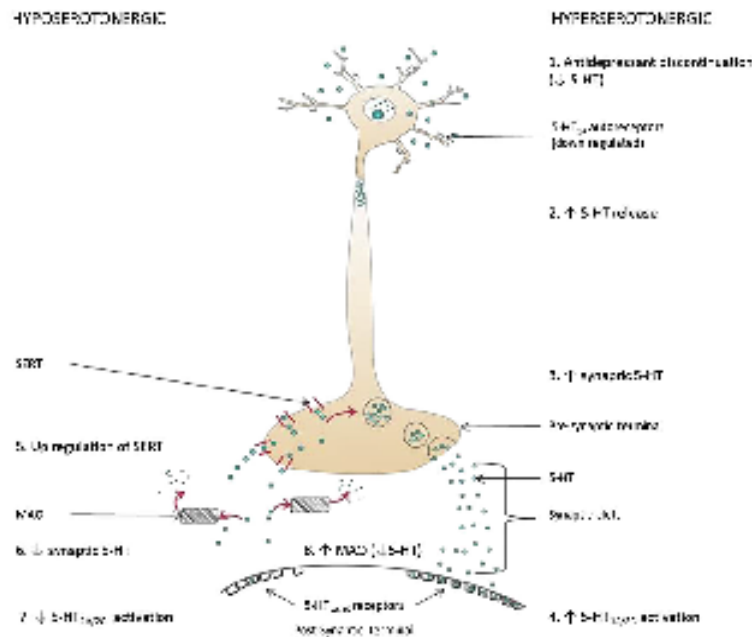


Figure 1. Synaptic serotonergic disturbances following antidepressant discontinuation syndrome (ADS). *Hyperserotonergia*: (1) Somatodendritic 5-HT<sub>1A</sub> receptors are down-regulated following chronic antidepressant use and successful remission of depression. Antidepressant discontinuation results in a decrease in 5-HT at the cell body. (2) This plus the down-regulated state of 5-HT<sub>1A</sub> autoreceptors disinhibits 5-HT release at the end synapse. (3+4) The resulting hyperserotonergia and excessive activation of postsynaptic 5-HT<sub>1A/2C</sub> receptors mediates disturbances in circadian rhythms, sleep disturbances and other symptoms of ADS. *Hyposerotonergia*: (5+6+7) Gradual recovery of 5-HT transporter (SERT) activity following antidepressant discontinuation decreases synaptic 5-HT and reduces post-synaptic activation of 5-HT<sub>1A/2C</sub> receptors. (8) Elevation in monoamine oxidase (MAO) activity evident in depression also influences the interplay between hyperserotonergia versus hyposerotonergia

receptor density, but especially SERT, plays a deciding role in the development of ADS. The earlier-noted elevation in MAO activity evident in depression and in patients in remission will almost certainly also influence the final somatodendritic versus synaptic levels of 5-HT and, in concert with the subsequent interplay between 5-HT<sub>1A</sub> receptors and SERT, will determine whether a postsynaptic hyposerotonergia or hyperserotonergia prevails (Figure 1).

Whatever the sequence of events, it is clear that stabilizing 5-HT transmission by targeting presynaptic 5-HT autoreceptors may be useful in preventing ADS. Although targeting a specific receptor to treat ADS seems futile, there may be value with regard to certain subsets of symptoms if a suitable pharmacological tool is available, for example ritanserin to address excessive 5-HT<sub>2</sub>-mediated manifestations. 5-HT plays a central role in antidepressant action (Stahl, 2013), while it is clear from earlier discussion that 5-HT also plays a contributory role in the risk and development of ADS. Because antidepressants are designed to increase synaptic levels of 5-HT, the risk for ADS appears to be inseparable from how antidepressants work. Nevertheless, we would like to argue that *curbing or not promoting*

*5-HT release* in the first place would constitute an effective strategy to limit the risk of ADS without compromising antidepressant efficacy. Indeed, there is clinical evidence to corroborate this argument.

#### LESSONS LEARNED WITH AGOMELATINE

Despite the realization that depression is a multifactorial illness, and that targeting 5-HT is not the ultimate neurobiological target for antidepressant action, 5-HT remains key to the behavioural pathology of the illness and is a central construct upon which currently marketed antidepressants work (Lang and Borgwardt, 2013; Stahl *et al.*, 2013). However, there is one exception. Agomelatine is a novel first-in-class antidepressant with a non-monoaminergic mechanism of action (De Bodinat *et al.*, 2010), acting as a melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptor agonist and a neutral 5-HT<sub>2C</sub> receptor antagonist (Fornaro *et al.*, 2010; Demyttenaere, 2011; Guardiola-Lemaire *et al.*, 2014). Its antidepressant activity is dependent on the synergy between MT<sub>1</sub> and MT<sub>2</sub> receptor agonism and 5-HT<sub>2C</sub> antagonism, particularly in the suprachiasmatic nucleus (SCN) that allows re-entrainment of altered biological rhythms

known to be dysregulated in depression (Racagni *et al.*, 2011). Agomelatine can target mood, anxiety and cognitive behaviours involved in depression by either *directly* binding to 5-HT<sub>2C</sub>/MT receptors throughout the brain or do so *indirectly* by targeting the SCN, and from there modifying presumably glutamate output from the SCN (Abrahamson and Moore, 2001) that impact on monoaminergic cell bodies in the brain stem and hence modify DA, NA and 5-HT release in distal brain regions (Chenu *et al.*, 2013; McClung, 2013). Given the important role for dysregulation of the HPA axis in depression (Harvey *et al.*, 2003) and the role of the circadian system in regulating these HPA-axis hormones and peptides, these combined actions will play an important role in agomelatine's mechanism of action.

However, while agomelatine increases 5-HT after chronic dosing (Chenu *et al.*, 2013), unlike the TCAs, SRIs and SNRIs, it *does not* induce an acute increase in synaptic 5-HT (Millan *et al.*, 2003; Chenu *et al.*, 2013) and does not have any noteworthy affinity for other neuroreceptors, including adenosine, NA<sub>1</sub>ergic, DA<sub>1</sub>ergic, GABA, muscarinic, nicotinic, histamine, excitatory amino acid, benzodiazepine and sigma receptors, as well as sodium, potassium and calcium channels (Guardiola-Lemaitre *et al.*, 2014). Furthermore, clinically, it is not associated with ADS after discontinuation (Chanrion *et al.*, 2008; Aloyo *et al.*, 2009). We have earlier argued that ADS is related to the release of 5-HT by the antidepressant and subsequent long-term effects on 5-HT<sub>1A/2C</sub> receptors, SERT and MAO density (Figure 1). In keeping with its inability to provoke 5-HT release, agomelatine does not alter 5-HT<sub>1A</sub> receptor density (Millan *et al.*, 2003). In fact, neither acute nor chronic agomelatine administration in rats alters the density of limbic 5-HT<sub>1A</sub> receptors or their coupling with G proteins (Hanoun *et al.*, 2004). Together, this translates into less perturbation of serotonergic function than that achieved with SRIs, SNRIs etc., and as a result, this is less likely to evoke ADS. Additionally, antidepressants more often decrease 5-HT<sub>2C</sub> receptor signalling (Martin *et al.*, 2014) so that discontinuation and an associated up-regulation of 5-HT<sub>2C</sub> receptors may mediate many of neuropsychiatric manifestations of ADS. Following on this, studies have shown that agomelatine does not increase the cell surface density and sensitivity of 5-HT<sub>2C</sub> sites (de Bodinat *et al.*, 2010; Guardiola-Lemaitre *et al.*, 2014). Interestingly, fluoxetine, an SSRI known not to evoke ADS, is also a 5-HT<sub>2C</sub> receptor antagonist (Sánchez and Hyttel, 1999), although it is argued that agomelatine's *neutral* antagonistic properties at this receptor are more relevant here (see Guardiola-Lemaitre *et al.*, 2014, for review). Theoretically at least, agomelatine-associated blockade

of 5-HT<sub>2C</sub> receptors may also temper the untoward effects of 5-HT<sub>2C</sub>-mediated events following antidepressant withdrawal (less so for effects mediated by other 5-HT receptors), possibly of value when switching from an SRI/SNRI to agomelatine. Considering its low binding to the muscarinic receptor, agomelatine will not provoke cholinergic overdrive, which is also purported to be responsible for ADS and to precipitate relapse.

The pharmacokinetic profile of agomelatine is also relevant. Earlier, it was stated that the risk of ADS is inversely related to the T<sub>1/2</sub> of the antidepressant. Agomelatine is extensively metabolized by cytochrome P450, and isoforms 1A1, 1A2 and 2C9 (De Bodinat *et al.*, 2010; Fornaro *et al.*, 2010), has a moderate volume of distribution (35 L), is 85–95% bound to plasma proteins (Fornaro *et al.*, 2010), and is eliminated mainly by urinary excretion (Dolder *et al.*, 2008). Importantly, it has a T<sub>1/2</sub> of 2.5 h (Dolder *et al.*, 2008; De Bodinat *et al.*, 2010), markedly less than other antidepressants (Table 2), while its major metabolite, 3-hydroxy-7-desmethyl-agomelatine, has a low affinity for MT<sub>1</sub>, MT<sub>2</sub> and 5-HT<sub>2C</sub> receptors. These pharmacokinetic characteristics suggest a short period of receptor occupancy and a rapid elimination after discontinuation, placing it firmly in the "high risk" category for inducing ADS. Moreover, these apparently negative attributes suggest a greater risk of breakthrough depressive symptoms than other antidepressants because of a lack of sustained binding to its neurobiological target, unless multiple daily dosing is applied. Nevertheless, as noted earlier, agomelatine has as yet not been associated with ADS (Chanrion *et al.*, 2008; Aloyo *et al.*, 2009), while 25–50 mg agomelatine once daily is as effective an antidepressant as comparator antidepressants (Kennedy and Rizvi, 2010). Despite the reasons already described earlier validating its low risk for inducing ADS, the latter paradox prompts further discussion on the pharmacokinetic and pharmacodynamic characteristics of agomelatine.

#### *Reduced antidepressant discontinuation syndrome and agomelatine: Pharmacokinetics*

Unlike SRIs and SNRIs that rely on sustained occupancy of the SERT for clinical efficacy (Bymaster *et al.*, 2001), agomelatine presents more with phasic binding to M<sub>1</sub>/M<sub>2</sub> and 5-HT<sub>2C</sub> receptors that is closely correlated with its obligatory dosing at night. This amounts to a 5-HT receptor binding profile that is more physiological, allowing endogenous 5-HT to bind to its receptor in an appropriate manner during the day, especially in other brain regions where persistent antagonistic binding to 5-HT<sub>2C</sub> receptors could result in anti-serotonergic side effects. Indeed, unlike M<sub>1/2</sub> receptors, the expression of non-SCN 5-HT<sub>2C</sub> receptors

is not affected by circadian rhythm (Lam, 2006), implying that prolonged occupancy of these receptors is wholly determined by the pharmacokinetic properties of the drug and how long it stays bound to the receptor. The short  $T_{1/2}$  of agomelatine and its phasic binding to  $M_1/M_2$  and 5-HT<sub>2C</sub> receptors seems to be key to promoting normal "burst firing" of the SCN and pineal gland that is more physiological than that achieved by constant long-term occupancy of these receptors by a typical 5-HT<sub>2AC</sub> or  $M_1/M_2$  active drug. This not only benefits the more effective functioning of the SCN–pineal gland complex, especially with dosing at the start of the dark cycle, but will also prevent non-physiological synaptic activity mediated by prolonged anti-serotonergic activity in other brain regions, such as sexual dysfunction and weight gain (Dolder *et al.*, 2008). Furthermore, phasic receptor binding will maintain appropriate physiological functioning of the target system across all signalling networks and will not induce reactive adaptive changes to autoreceptors, postsynaptic receptors and reuptake transporters, and, in this manner, limit the risk of ADS as well as other adverse effects. Although the more physiological actions of agomelatine may preclude it from causing ADS compared with other antidepressants while its efficacy is similar, this argument, also by implication, suggests that the efficacy of the latter agents could be underestimated as a result of non-compliance and ADS.

#### *Reduced antidepressant discontinuation syndrome and agomelatine: Pharmacodynamics*

Agomelatine selectively targets  $MT_1$ ,  $MT_2$  and 5-HT<sub>2C</sub> receptors (Fomaro *et al.*, 2010; Demyttenaere, 2011; Guardiola-Lemaître *et al.*, 2014). Melanergic receptors are widely distributed in the brain with the highest density of  $MT_1$  and  $MT_2$  receptors found in the SCN and pars tuberalis, but also located in the frontal cortex (FC), prefrontal cortex (PFC), cerebellar cortex, basal ganglia, substantia nigra, hippocampus (HPC), ventral tegmental area (VTA), nucleus accumbens, thalamus and the retina (Hardeband *et al.*, 2011; Tardito *et al.*, 2012). The presence of melatonin receptors in the SCN describes its direct action where, together with serotonin (via 5-HT<sub>2C</sub> receptors), it establishes the biorhythms of the master clock that in turn modifies brain stem monoamine release. Its presence in other limbic brain regions suggests a central role for melatonin in circadian regulation of regional brain function, such as hippocampal plasticity (Chaudhury *et al.*, 2005) and the circadian pattern of clock gene expression in hippocampal neurons (Wakamatsu *et al.*, 2001; Jilg *et al.*, 2010). Both  $MT_1$  and  $MT_2$  receptors are 7-transmembrane, G protein-coupled receptors acting via Gi

proteins (Tardito *et al.*, 2012). The  $MT_1$  receptor is negatively coupled to adenylyl cyclase (AC), thereby negatively modulating protein kinase A cAMP response element binding protein signalling and phospholipase C $\beta$  activation, which is central to antidepressant activity (Manji *et al.*, 2001; Krishnan and Nestler, 2008).  $MT_2$  receptors, on the other hand, are positively coupled to AC while being negatively coupled to guanylyl cyclase (GC), thus inhibiting the NO-cyclic guanosine monophosphate (cGMP) pathway (Von Gall *et al.*, 2002; Srinivasan *et al.*, 2012; Tardito *et al.*, 2012). By exerting a stimulatory effect on the  $MT_2$  receptor, agomelatine will abrogate NO-cGMP signalling that may have relevance for antidepressant response (Dhir and Kulkarni, 2011). The expression of melatonin receptors, particularly in the SCN, shows a diurnal rhythmicity and is regulated by daylight and the internal clock (Tardito *et al.*, 2012). Despite the presence of  $M_1$  and  $M_2$  receptors in important limbic brain regions, melatonin alone is not able to modulate DA, NA and glutamate release, or effect an adequate antidepressant response, thus emphasizing the important role of 5-HT<sub>2C</sub> receptors in this regard (Millan *et al.*, 2003; Tardito *et al.*, 2010) and of their combined role in agomelatine's antidepressant effects (Millan *et al.*, 2003; Norman, 2012).

5-HT<sub>2C</sub> receptors enjoy a similar distribution as  $MT_1$  and  $MT_2$  receptors (Tardito *et al.*, 2012), although the majority of 5-HT<sub>2C</sub> receptors are somatodendritic heteroreceptors located on GABAergic, glutamatergic and dopaminergic neurons. 5-HT<sub>2C</sub> receptors are also expressed by GABAergic interneurons in the raphe nuclei and in the ascending noradrenergic and dopaminergic pathways. Tonic release of 5-HT and activation of 5-HT<sub>2C</sub> receptors therefore excites GABAergic neurons in the brainstem, triggering tonic inhibition of both NA and DA release in the PFC (Millan *et al.*, 2003; De Berardis *et al.*, 2011). Its modest affinity for 5-HT<sub>2C</sub> receptors alone is not responsible for its antidepressant effects (Millan *et al.*, 2003), but by blocking extra-SCN-located 5-HT<sub>2C</sub> receptors in monoaminergic cell bodies in the brain stem, agomelatine disinhibits frontal cortical DA and NA release, and, in this way, engenders procognitive and antidepressant effects. 5-HT<sub>2C</sub> receptors also follow a circadian rhythm in the SCN and in the HPC with gradually increasing expression in the afternoon that peaks in the early morning (reviewed in Racagni *et al.*, 2011; Tardito *et al.*, 2012). Interestingly, expression of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors is not affected by the circadian rhythm (Lam, 2006). Through positive coupling to Gq/G<sub>11</sub> proteins, 5-HT<sub>2C</sub> receptors lead to phospholipase C activation and the generation of inositol triphosphate and an increase in intracellular calcium (Jensen *et al.*, 2010; Tardito *et al.*, 2012).

When considering these actions in the context of ADS, anxiety-like manifestations are evident in both humans experiencing ADS and antidepressant discontinuation models in animals (Table 1). That excessive activation of the 5-HT<sub>2C</sub> receptor is anxiogenic (Heisler *et al.*, 2007), and that 5-HT<sub>2C</sub> receptor antagonists are rapid acting anxiolytics with sustained effects (Dekeyne *et al.*, 2008), provides robust support that agomelatine will have anxiolytic actions (Figure 2). Indeed, this has been corroborated in the pre-clinical (Papp *et al.*, 2006) and clinical literature (Stein, 2008; Kasper *et al.*, 2010; Stein *et al.*, 2013). Moreover, by *not* provoking release of 5-HT in the first place agomelatine will not be anxiogenic when initiating treatment, while the absence of long-term effects on SERT and 5-HT<sub>1A</sub> receptor density will prevent ADS-associated hyperserotonergia and anxiety in the event of discontinuation (Figure 1). Furthermore,  $\alpha_2$ -mediated suppression of 5-HT, DA and glutamate release via facilitation of NA release in the frontal cortex, amygdala, periaqueductal grey, hippocampus and the nucleus accumbens may extend its anxiolytic capabilities (Millan, 2003; Figure 2).

Antidepressant discontinuation in animal models has revealed a possible role for altered glutamate activity in ADS (Harvey *et al.*, 2002b), while agomelatine prevents depolarization-evoked glutamate release in a 5-HT<sub>2C</sub>-dependent and MT<sub>1</sub>/MT<sub>2</sub>-dependent manner (Musazzi *et al.*, 2010; Tardito *et al.*, 2010). Animal models of ADS have noted the involvement of glutamate (Harvey *et al.*, 2002) as well as an increase in NO-cGMP signalling following discontinuation (Harvey *et al.*, 2006). MT<sub>2</sub> receptors inhibit soluble GC (Von Gall *et al.*, 2002; Srinivasan *et al.*, 2012), so by activating the MT<sub>2</sub> receptor, agomelatine will abrogate NO-cGMP signalling that may have relevance in reducing ADS. By increasing NA-mediated activation of  $\alpha_2$ -heteroreceptors on glutamate neurons (Figure 2), agomelatine will also reduce glutamate release, thereby modifying a number of glutamate-dependent targets, in particular the NO-cGMP system and other events involved in neuroplasticity. If antidepressant non-compliance is persistent, such neuroplastic events may in the end compromise long-term outcome (Harvey *et al.*, 2003).

Finally, animal studies have suggested that ADS may involve effects on the dopaminergic system

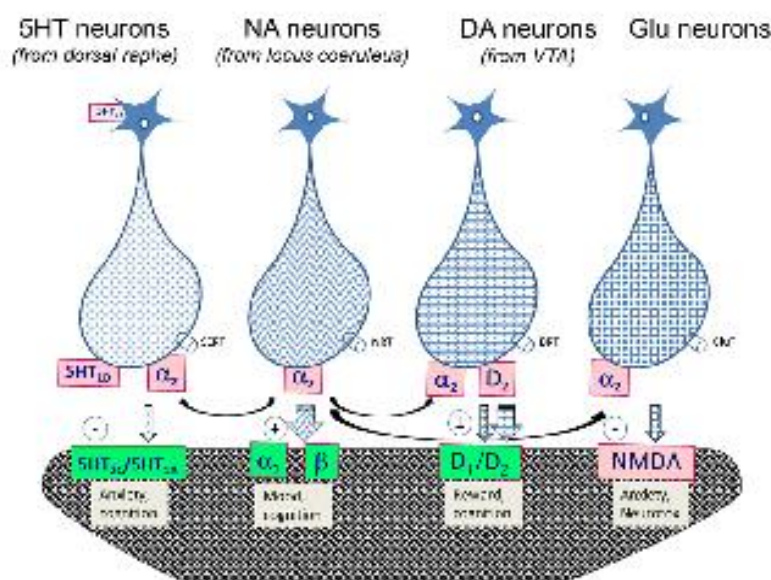


Figure 2. Schematic representation depicting the actions of agomelatine on its primary (green) and secondary (pink) targets that describes its unique pharmacological action as an antidepressant devoid of antidepressant discontinuation syndrome (ADS) risk. Agomelatine's mechanism of action largely excludes serotonergic actions, firstly by not releasing 5-HT and then by blocking post-synaptic 5-HT<sub>2C</sub> receptors, thus preventing up-regulation of SERT and somatodendritic 5-HT<sub>1A</sub> receptors. The absence of hyperserotonergia limits complications such as agitation and anxiety. Furthermore, agomelatine specifically promotes noradrenergic and dopaminergic activity where its direct dopaminergic actions can be noted in the frontal cortex as an improvement in mood and cognition, while its secondary actions include  $\alpha_2$ -mediated suppression of 5-HT, dopamine (DA) and glutamate release in the frontal cortex, amygdala, periaqueductal grey, hippocampus and the nucleus accumbens (Millan, 2003). The latter actions extend its capabilities to include anxiolysis, anti-anhedonic and neuroprotective actions. The short-term occupancy of its target receptors (*viz.* 5-HT<sub>2C</sub> and M<sub>1</sub>/M<sub>2</sub>) also allow for less non-physiological modification of these signalling systems with a lesser likelihood of discontinuation-related sequelae, especially that related to 5-HT and glutamate (refer to text for further description). SERT, 5-HT transporter; NRT, noradrenaline (NA) transporter; DRT, DA transporter; GluT, glutamate transporter

(Gardier *et al.*, 1994; Renoir, 2013), especially symptoms of anxiety, low mood and tearfulness (Table 1). By creating the expectation of reward that will drive a positive affective state (pleasure, motivation, drive and motivation), the mesolimbic DA pathway plays a prominent role in depression and antidepressant response (Collu *et al.*, 1997; Boyer *et al.*, 2000; Liu *et al.*, 2008; Lane, 2014). It is of interest then that SRIs (by releasing 5-HT) adversely affect the neural processing of rewarding and aversive stimuli (Alén *et al.*, 2013), possibly resulting in down-regulation of the reward system (Lane, 2014). Clinically, SRIs are less effective in managing the anhedonic symptoms of depression (Nutt *et al.*, 2007; Lane, 2014) and in fact provoke cognitive and emotional blunting (Sansone and Sansone, 2010). These SRI-associated effects have been ascribed to 5-HT<sub>2C</sub>-mediated suppression of frontal DA function (Bamhart *et al.*, 2004; Wongpakaran *et al.*, 2007; McCabe *et al.*, 2010; Sansone and Sansone, 2010) (Figure 2). By not promoting 5-HT release, agomelatine will bolster and/or sustain DA function (by limiting 5-HT<sub>2C</sub> activation of GABA inhibitory neurons), or it can temper DA release via NA activation of  $\alpha_2$ -heteroreceptors on DA neurons (Figure 2). Another explanation involves its neutral antagonistic effects on 5-HT<sub>2C</sub> receptors, which are constitutively active in the brain (Guardiola-Lemaitre *et al.*, 2014). This action suggests that agomelatine normalizes but does not suppress basal 5-HT<sub>2C</sub> activity, allowing it to accelerate fronto-cortical dopaminergic transmission without affecting accumbal or striatal DA and NA levels (Guardiola-Lemaitre *et al.*, 2014). Acute administration of agomelatine also selectively increases NA<sub>1</sub> firing in the locus coeruleus without affecting DA<sub>1</sub> neurons in the VTA (Guardiola-Lemaitre *et al.*, 2014). These conservative actions on the DA reward pathways may underlie its beneficial effects on positive reward processing and allow it to improve anhedonia (Di Giannantonio *et al.*, 2011) without inducing emotional blunting (Martinotti *et al.*, 2012). With ADS having the potential to induce a stress response (Michelson *et al.*, 2000; Harvey *et al.*, 2003), while over-stimulation of the stress-system down-regulates the reward system (Lane, 2014), agomelatine's action on these pathways may also minimize the risk of ADS post-discontinuation. Finally, its short T<sub>1/2</sub> will only allow transient effects on DA signalling in these circuits unlike the more sustained effects of an SRI.

#### CONCLUDING REMARKS

The ADS has major clinical significance. Not only can it lead to mismanagement of the disorder, but what is

often not realized is its effects on long-term outcome. Experimental data regarding the neurobiology and pharmacological mechanisms underlying ADS are scant. What is nevertheless evident in both clinical and preclinical studies is that inappropriate antidepressant discontinuation engenders a bio-behavioural stress response that, in an already compromised individual, may have far reaching negative effects on long-term treatment response and outcome. Moreover, some of the biological processes set in motion are well known for their involvement in neuroplasticity as well as neurotoxicity if excessively activated, such as glutamatergic and nitroergic pathways that explain the association between repeated antidepressant discontinuation and treatment resistance and/or relapse. Although not definitive, aberrant 5-HT release is the primary mediator of ADS, especially via actions on SERT, 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors. However, cholinergic, DA<sub>1</sub>ergic and other mechanisms cannot be ignored. We propose that either hyperserotonergia or hyposerotonergia may underlie the syndrome. What this review has attempted to consolidate is that ADS may be exclusively a problem of acute 5-HT release evoked by antidepressants such as SRIs, SNRIs, TCAs and some atypical compounds leading to changes in 5-HT homeostasis. By using agomelatine as a counterpoint to this argument, it is now evident that an effective antidepressant need not engender a risk for ADS. Indeed, what is clear is that non-physiological or uncontrolled elevations in 5-HT may be counter-productive, so that antidepressants devoid of direct acting serotonergic effects may in the long run be conducive to a more successful outcome. The unique pharmacodynamic and pharmacokinetic profile of agomelatine may hold the key towards intuitive and rational drug design of an antidepressant that targets serotonergic signalling in a physiologically appropriate manner, yet that does not evoke ADS upon discontinuation. New research into establishing whether these properties are indeed linked to agomelatine's beneficial clinical profile with regard to ADS needs to be undertaken. While these ideas require rigorous testing, they are provocative to new research in the area, and indeed raise the awareness of the long-term negative aspects of non-compliance and inappropriate antidepressant discontinuation.

#### CONFLICTS OF INTEREST

The authors declare that over the past 3 years, Brian Harvey has participated in speakers/advisory boards and received honoraria from Servier, and has received research funding and/or compound from Lundbeck and Orion Pharma. The authors declare that, except for income from the primary employer, research funding

to BHH from the South African Medical Research Council as well as the honoraria described earlier, no other financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional services, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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## AUTHOR CONTRIBUTIONS

B. H. Harvey devised the concept and wrote the first draft of the manuscript; F. N. Slabbert co-wrote the pre-submission draft of the manuscript. Both authors prepared the final version for publication.

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## CHAPTER 3: MANUSCRIPT 3.2

In this chapter, a manuscript titled

“Prospective analysis of the Medicine Possession Ratio (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011)”

is presented. The paper was submitted to the **South African Medical Journal** as a full-length research report, and prepared according to the specific *Instructions to the Author* for this journal (provided in Addendum B). The references for this manuscript are provided at the end of this chapter.

This manuscript has been published online. DOI:10.7196/SAMJ.8394.

Instructions to the author can be viewed with the following link:

<http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines> Date of access: 11 May. 2014.

## 3.2 Article 2

### Title

**Prospective analysis of the Medicine Possession Ratio (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011)**

Running Title

Medicine Possession Ratio of antidepressants

### AUTHORS

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### KEY WORDS

Antidepressants, compliance, medicine possession ratio, major depressive disorder, South Africa.

### KEY POINTS

- Patient compliance with antidepressants in the South African private health sector matched the global picture.
- The medicine treatment period of antidepressants had a significant influence on the medicine possession ratio.
- Gender is a weak predictor of ambulatory patient compliance with antidepressants.
- Elderly patients appeared more compliant with antidepressant medication,
- Newer generation antidepressants display the best compliance profile,
- The use of medicine claims data appears to be a feasible and reliable method to assess medicine possession ratios and compliance with antidepressants.

## **CONFLICT OF INTEREST**

Brian Harvey has participated in speakers/advisory boards and received honoraria from Organon, Pfizer and Servier, and has received research funding from Lundbeck and Servier. Except for income from the primary employer and research funding to BHH from the South African Medical Research Council, and the exceptions noted earlier, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional services, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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WORD COUNT: 2898

## **ABSTRACT:**

**Background:** Major depressive disorder (MDD) is a disabling mental illness with a high morbidity and mortality. Inadequate efficacy of treatments, unfavourable side effect profiles, and consequently shortfalls in non-compliance are major stumbling blocks in the treatment of MDD. Non-compliance data in low-to-middle income countries is lacking.

**Objective:** We investigated the prevalence of antidepressant non-compliance in the private health care sector of South Africa.

**Methods:** We conducted a prospective, cohort study, analysing antidepressant (AD) medicine claims (N = 35175) for 14 135 patients, obtained from a nationally representative Pharmaceutical Benefit Management (PBM) company, over a 6 year study period, viz. 1 January 2006 to 31 December 2011. The medicine possession ratio (MPR) was used as proxy to determine patient compliance with AD medication. The following inclusion criteria were applied: only patients older than 18 years and treatment initiated by a psychiatrist following an appropriate ICD-10 diagnosis of a mood disorder. A patient was considered compliant with his/her AD treatment if the  $MPR \geq 80\% \leq 110\%$  plus > 4 month treatment period.

**Results:** After the first 4 months only 34% of patients were compliant. A statistically significant association was found between active ingredient consumed and compliance ( $p < 0.0001$ ). Only 26.2% of patients who received amitriptyline-containing products were compliant compared to 38.8% and 38.7% in the cases of venlafaxine and duloxetine, respectively.

**Conclusion:** The compliance data collected from pharmacy claims provides a workable estimate of the broader clinical scenario it represents. Although differences were evident between classes of AD, non-compliance was found to be high in the private health care environment of South Africa, comparable with global trends.

## INTRODUCTION

Major depressive disorder (MDD) is disabling illness affecting people worldwide. The lifetime prevalence for major depression in South Africa is 9.8%<sup>[1]</sup> compared to 16.7%<sup>[2]</sup> and approximately 13% for the USA and Europe, respectively.<sup>[3]</sup> MDD not only decreases general health, but also impairs quality of life, performance at work, school and everyday social interactions. MDD poses a substantial risk for suicide,<sup>[4]</sup> with an estimated 15–20% mortality rate.<sup>[4]</sup> The economic impact of affective disorders in Europe (major depression and bipolar depression) amounts to € 106 billion (2004 figures).<sup>[5]</sup> Of this amount, nearly € 29 billion was spent on direct health care costs such as hospitalization, visits to doctors and drug treatment, whereas € 77 billion was due to indirect costs including premature death, sick leave, and workdays lost.<sup>[5]</sup> The economic cost of depressive disorders in the United States in 2007 was estimated to be over \$ 83 billion,<sup>[6]</sup> with direct and indirect costs on health expenditure of \$ 26 billion and \$ 57 billion, respectively. Projections done in 2011 indicated that the total annual cost to South Africans living with severe depression and anxiety disorders amounted to \$3.6 billion.<sup>[7]</sup> These estimates indicated either that mental illness has a major economic impact, through the effect of disability and stigma on earnings, or that people in lower income groups are at increased risk of mental illness.

The management of MDD is severely compromised by non-compliance.<sup>[8]</sup> Treatment of depression is recommended to continue for at least four to six months from the time of remission, to prevent relapse.<sup>[9,10]</sup> This is extended in high risk patients, those with recurrent illness and/or those with a history of treatment resistance. Several studies have shown that the remission of compliant patients with depression is higher than for non-compliant patients,<sup>[11,12]</sup> and furthermore that sustained antidepressant (AD) use over 12 to 36 months may further decrease the risk of relapse by up to 70% compared to non-compliant patients.<sup>[13]</sup> In a Spanish study, 56% of patients discontinued their AD treatment within the first four months, whereas only 22% maintained satisfactory adherence over the period of 5 years.<sup>[14]</sup> Many studies concur that between 30 to 60% of patients do not comply with AD treatment<sup>[15,16]</sup> and that up to 30% of patients are likely to stop taking ADs within the first month after the start of treatment. In addition 45–60% of patients will have stopped their prescribed treatment by the end of the third month.<sup>[17-19]</sup> Without adequate treatment, patients may experience further relapses of depressive episodes.<sup>[20]</sup> Furthermore, preclinical studies demonstrate that premature discontinuation may evoke a specific sequence of neurobiological events that underlie relapse and treatment resistance.<sup>[21,22]</sup> Thus, compliance and persistence are key concerns in the pharmacological management of MDD. No studies have investigated AD compliance in low-to-middle income countries. We have therefore studied the prevalence of non-compliance of AD treatment in the private health care sector in South Africa (SA), using the MPR (Medicine possession ratio) as a proxy for patient compliance with ADs, also looking at possible change in the prescribed daily dosage (PDD) between compliant and non-compliant patients, and whether class of AD is an additional determinant.

## METHODS

We conducted a prospective, descriptive, cohort study analysing nationally representative medicine claims data submitted to a privately owned South African Pharmaceutical Benefit Management (PBM) company. The database included all prescriptions for an AD (Monthly Index of Medical Specialities classification: 1.4)<sup>[23]</sup> for 407 586 patients over a 6-year study period, viz. 1 January 2006 to 31 December 2011.

We extracted data for patient demographics (gender and date of birth) and pertinent prescription information (such as drug trade name, days supplied, dispensing date, quantity of medicine prescribed,

initial dose, final dose and ICD-10 code per claim). The quality of data was ascertained by several automated validation processes that were applied by the PBM. There were no missing data fields in the data sets. The variables 'birth date' and 'dispensing date' were used to calculate the age of patients on the date of treatment and the number of days between refills.

A study population was selected according to the inclusion criteria illustrated in Figure 1. The ICD-10 codes are based upon the *International Classification of Diseases*, 10<sup>th</sup> edition published by the World Health Organization (WHO).<sup>[24]</sup> In this study the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist. Thereby, it was ensured that data were excluded where ADs may have been used for other illnesses, such as amitriptyline used for the treatment of chronic pain. The study population were older than 18 years.

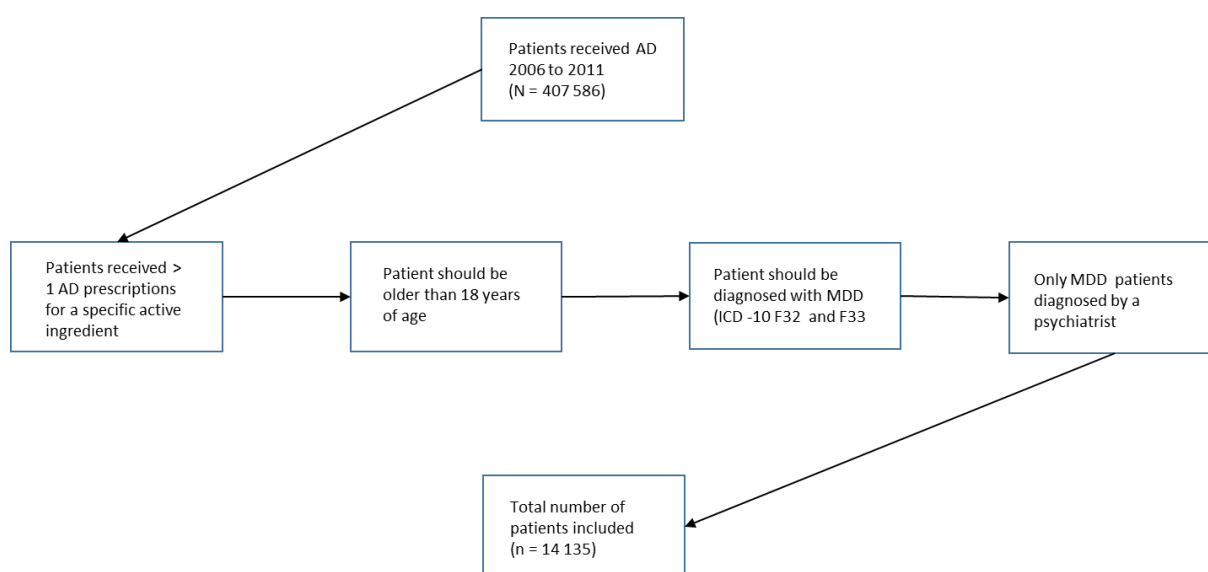


Figure 1. The inclusion criteria used in this study.

The study population consisted of a total number of 14 135 patients receiving 35 175 AD medicine items dispensed on more than two occasions.

The medicine possession ratio (MPR) is a well-established method of calculating drug compliance in pharmcoepidemiological studies, including chronic diseases such as depression<sup>[14]</sup>, hypertension<sup>[25]</sup> osteoporosis<sup>[26]</sup> and schizophrenia.<sup>[27]</sup> However, it is important to note that the compliance value obtained from the MPR only gives an indication of the possession of medicine by the patient, and that appropriate consumption of medicine is assumed to ensue from possession. The usage of medicine claims data to determine in MPR calculations is useful in that it is acceptably accurate, convenient, objective, non-invasive and relatively inexpensive to obtain when a large study population is needed. It is therefore suitable for the calculation of MPR as an indication of patient compliance with medication therapy.

The MPR is defined as the total number of days for which medication is supplied (medicine treatment period), divided by the number of days in the refill interval, multiplied by 100.<sup>[28,29]</sup>

The MPR is considered acceptable if the calculated value is  $\geq 80\%$ , but  $\leq 110\%$ .<sup>[14]</sup> An MPR of less than 80% indicates the presence of refill gaps so that possession is considered unacceptably low (undersupply), whereas an MPR greater than 110% is considered unacceptably high (oversupply).

Data management and analysis was performed in SAS Version 9.1.3 (SAS Institute, Cary, NC).<sup>[30]</sup> All statistical significance was considered with probability of  $p < 0.05$ . The practical significance of the results was computed when the  $p$ -value was statistically significant ( $p \leq 0.05$ ).

For the purpose of this study the MPR and the medicine treatment period was used to determine AD compliance of patients. In order to treat MDD effectively and to prevent relapse, patients must be on chronic treatment for at least 120 days or more.<sup>[9,10,28]</sup> Therefore, all patients with MPR  $< 80\%$  or MPR  $> 110\%$  and/or an AD treatment period  $< 120$  days were deemed non-compliant. Conversely, a patient was considered compliant with his/her AD treatment if the MPR was  $\geq 80\%$  and  $\leq 110\%$  and the AD treatment period was longer than 120 days.

Variables (age, age groups, gender, treatment period, and active ingredients) were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations (SD) and 95% confidence intervals (CI). Patient's age was determined at time of first dispensing and divided into three groups: 18 to 40 years; 41 to 60 years; 61+ years. Treatment duration was calculated as the time (in days) from the first prescription for the ADs until the last. It was divided into three groups:  $\leq 30$  days;  $\geq 31$  and  $\leq 120$  days;  $> 120$  days).

Chi-square test ( $\chi^2$ ) was used to determine if an association exists between proportions of two or more groups (age groups vs. MPR groups). The Cramer's V statistics was used to test practical significance of this association. The two-sample  $t$ -test allowed us to compare the mean MPR of male and female patients. The one-way ANOVA was used to test differences between three or more means and to calculate differences in the adjusted PDD changes between compliant and non-compliant patients. It was operationalized with the General linear model (GLM) procedure of the SAS Version 9.1.3 system. If a difference was indicated, a Tukey multiple comparison test was performed to determine which groups most significantly influence the overall difference between groups. Cohen's  $d$  was used to evaluate effect size between means (with  $d \geq 0.8$  defined as practically significant).<sup>[31]</sup> \_ENREF\_33

The PDD (in mg) of an AD was calculated by multiplying the number of tablets (or volume of suspension or syrup) dispensed during the treatment period and the strength per tablet (or per ml), divided by the number of days supplied. Possible PDD changes, from the first until the last prescription on the database, were determined. The correlation coefficient,  $r$ , indicated a negative association between the initial PDD and change in PDD ( $r < -0.5$ ;  $p = 0.0001$ ). Therefore possible PDD changes were adjusted for variations in initial dosage.

This study was approved by the Ethics committee of the North-West University, Potchefstroom campus (NWU-0046-08-A5) and the boards of directors of the PBM. Data were analyzed anonymously.

## RESULTS

### Medicine possession ratios of antidepressants

The mean age of the patients was 50.4 (SD 15.9) years and 71.1% were women, 71.4% of the patients received AD medication for longer than four months (Table 1). The mean MPR of the 35 175 ADs were

98.2% (95%CI: 96.6–99.9) (Table 2). Only 50.8% of dispensed ADs were associated with an acceptable MPR of between 80% and 110% (Table 2).

Table 1. Patient demographics and medicine use data

	<b>n</b>	<b>%</b>
<b>Age (SD) (years)</b>	50.4(15.9)	
<b>Age groups( years)</b>		
> 18 and ≤ 40	3 449	24.0
> 40 and ≤60	6 537	46.0
> 60	4 149	30.0
<b>Gender</b>		
Female	10 003	71.0
Male	4 132	29.0
<b>Treatment period (days)</b>		
≤ 30	830	6.0
>30 to ≤ 120	3256	23.0
> 120	10 049	71.0
<b>Top ten active ingredients (Medicine items)</b>		
Venlafaxine	5 222	14.9
Escitalopram	5 117	14.6
Duloxetine	3 351	9.5
Mirtazapine	2 992	8.5
Citalopram	2 919	8.3
Fluoxetine	2 433	6.9
Bupropion	2 153	6.1
Sertraline	2 137	6.1
Amitriptyline	2 105	6.0
Trazodone	1 834	5.2
<b>Antidepressant medicine possession ratio</b>		
> 0 and < 80	12 490	34.3
≥ 80 and ≤ 110	17 876	50.8
> 110	5 250	14.9

No statistically significant differences were found between the MPR of male and female patients: 98.2% (95%CI: 98.2–96.2) vs. 98.4% (95%CI: 98.4–95.3) (Table 2). Patients older than 60 years had lower MPR than those aged 18 to 40 years ( $p = 0.0169$ ) (Table 2).

Table 2. Medicine possession ratios of antidepressants by age group, gender and treatment period.

Variable	n	Mean (%)	95% CI	p value
<b>Overall</b>	35 175	98.2	96.6–99.9	
<b>Age group (years)</b>				
> 18 and ≤ 40	7 419	102.4*	98.1–106.8	0.0169
> 40 and ≤ 60	16 911	98.0	95.7–100.4	
> 60	10 845	95.6*	93.0–98.3	
<b>Gender</b>				
Male	9 739	98.4	95.4–101.4	0.9200
Female	25 536	98.2	96.2–100.1	
<b>Treatment period (days)</b>				
≤ 30	2 769	255.4	235.7–275.1	0.0001
>30 to ≤ 120	9 208	94.1	93.3–94.9	
> 120	23 198	81.1	80.7–81.5	

Table 2 clearly indicates that the treatment period had a statistical ( $p = 0.0001$ ) and practical significant ( $d > 0.8$ ) influence on the MPR of ADs. An abnormally large number of patients were noted to be on treatment for less than 30 days (255.4% [95%CI: 235.7–275.1]). This increase in MPR was also practically significant compared to those on therapy between 30 and 120 days (94.1% [95%CI: 93.2–94.9]) and those on therapy for longer than 120 days (81.1% [95%CI: 80.7-81.5]) ( $d > 1.0$ ).

#### **Patient compliance with antidepressant therapy**

Only 34% of patients were compliant with the AD treatment. In the majority of cases (66%), the MPR were not in the acceptable range (80-110%) and the treatment period was less than 120 days (Table 3); thus deemed non-compliant.

Table 3. Patient compliance with antidepressants by age group, gender and active ingredient

Variable	Compliant		Non-compliant		p value
	n	%	n	%	
<b>Overall</b>	11 953	34.0	23 222	66.0	
<b>Age group (years)</b>	202	29.7	5 217	70.3	0.0001
> 18 and ≤ 40					
> 40 and ≤60	5 534	32.7	11 377	67.3	
> 60	4 217	38.9	6 628	61.1	
<b>Gender</b>					0.1342
Male	3 369	34.6	6 370	65.4	
Female	8 584	33.8	16 852	66.3	
<b>Top ten active ingredients</b>					0.0001
<b>Venlafaxine</b>	2 026	38.8	3 196	61.2	
<b>Escitalopram</b>	1 796	35.1	3 321	64.9	
<b>Duloxetine</b>	1 295	38.7	2 056	61.4	
<b>Mirtazapine</b>	862	28.8	2 130	71.2	
<b>Citalopram</b>	1 032	35.4	1 887	64.7	
<b>Fluoxetine</b>	763	31.4	1 670	68.6	
<b>Bupropion</b>	724	33.6	1 429	66.4	
<b>Sertraline</b>	701	32.8	1 436	67.2	
<b>Amitriptyline</b>	552	26.2	1 553	73.8	
<b>Trazodone</b>	602	32.8	1 232	67.2	

No statistical significant association was found between gender and patient compliance ( $p = 0.1342$ ). Of practical significance ( $p < 0.0001$ ; Cramer V = 0.0734), the results reveal that a larger percentage (38.9%) of patients older than 60 years receiving ADs, and who were likely to have chronic co-morbidities such as hypertension or diabetes, were compliant compared to those in the 18 to 40 years age group (Table 3).

The ten most dispensed AD medications represented 86.6% of all those dispensed during the study period (Table 1). These include venlafaxine, escitalopram, duloxetine, mirtazapine, citalopram, fluoxetine, bupropion, sertraline, amitriptyline and trazodone. A statistically significant association was found between the type of active ingredients consumed and compliance ( $p < 0.0001$ ) (Table 3). Only 26.2% of patients who received amitriptyline-containing products were compliant compared to 38.8% and 38.7% in the case of the ADs with the highest compliance, viz. venlafaxine and duloxetine, respectively (Table 3).

#### Changes in prescribed daily dosages (PDD) and compliance

Negative correlations between the initial PDD and PDD changes were found for all ADs ( $p = 0.0001$ ), with  $r > -0.5$  for venlafaxine, escitalopram, mirtazapine and amitriptyline. Statistically significant differences ( $p < 0.05$ ;  $d < 0.8$ ) in the adjusted PDD changes were found between complaint and non-compliant patients on venlafaxine, escitalopram, mirtazapine and amitriptyline therapy (Table 4). The mean decrease of an adjusted 6.7 mg (95%CI: -10.2– -3.2) in the PDD of venlafaxine in the non-compliant patient was

significantly different compared to the mean increase of 1.3 mg (95%CI: -3.2–5.6) in the compliant patient (Table 4). The PDD of mirtazapine also decreased with a mean adjusted 0.2 mg (95%CI: -1.2– -0.06) in the non-compliant patient, and with an adjusted mean increase of 1.2 mg (95%CI: 0.3 – 2) in the compliant patient (Table 4). Amitriptyline’s mean adjusted PDD also decreased with 1.3 mg (95%CI: -2.5 – -0.06) in the non-compliant patient and mean increase with 1.5 mg (95%CI: -0.5 – 3.6) in the compliant patient (Table 4. The mean PDD of escitalopram increased more in the compliant (1.7 mg, 95%CI: 1.2 – 2.2) than non-compliant (0.1 mg 95%CI: -0.3 – 0.5) patient group from the first prescription to the last prescription (Table 4).

Table 4. Adjusted for the change in initial antidepressant dosage in both compliant and non-compliant patients.

Top ten active ingredients	Compliant Patients			Non-compliant Patients			Compliant Patients		Non-compliant Patients			p value
	n	Initial PDD (mg)	Final PDD (mg)	n	Initial PDD (mg)	Final PDD (mg)	Adjusted change in dosage (mg)	95% CI	Adjusted change in dosage (mg)	95% CI		
Venlafaxine	1986	136.1	137.2	3179	135.9	129.3	1.2	-3.2 5.6	-6.7	-10.2 -3.2	0.006	
Escitalopram	1796	20.7	21.9	3321	19.7	20.1	1.7	1.2 2.2	0.1	-0.3 0.5	0.0001	
Duloxetine	1295	60.7	61.8	2056	56.3	57.3	3.9	2.0 5.9	1.7	0.1 3.2	0.08	
Mirtazapine	862	26.3	26	2126	25.1	24.7	1.2	0.3 2.0	-0.2	-1.2 -0.06	0.0007	
Citalopram	1012	26.5	29.1	1871	28.7	29.1	2.4	1.5 3.3	1.5	0.8 2.2	0.12	
Fluoxetine	731	32.9	33	1654	33	33.1	0.8	-0.5 2.1	0.5	-0.4 1.4	0.76	
Bupropion	724	235	242.8	1429	238.6	246.7	27.0	11.2 42.8	26.8	16.5 37.1	0.98	
Sertraline	675	78.7	82.6	1418	80.5	84.4	5.8	3.6 8.1	5.7	4.1 7.2	0.90	
Amitriptyline	522	43.2	43.3	1553	40.6	37.9	1.5	-0.5 3.6	-1.3	-2.5 -0.06	0.02	
Trazodone	602	274.6	284.2	1232	390.7	362.5	-13.9	-34.8 7.0	4.2	-10.4 18.8	0.16	

## DISCUSSION

The most important findings of this study are that i) compliance with chronic AD treatment is poor (34%) in the SA private health care population, and ii) the use of medicine claims data may be a feasible and reliable method to assess medicine possession ratios and subsequent compliance with ADs.

Non-compliance in patients taking ADs is a major concern. A 34% compliance ratio described here is especially poor, although Bambauer et al.<sup>[32]</sup> found that 42% of patients stopped their treatment within the first 30 days and by day 90, 72% of patients had done so. This study not only emphasizes non-compliance as a major obstacle in the successful management of MDD, but to our knowledge, demonstrates for the first time that this hindrance to a successful outcome is evident in a middle-income country and is comparable to data reported for developed countries. Interestingly, this observation has prompted studies geared to isolating possible reasons for the poor compliance,<sup>[15,33,34]</sup> such as feeling better, side effects, fear of addiction and lack of efficacy.<sup>[33]</sup>

This study found the prevalence of MDD in female patients to be almost double that of males, and in keeping with previous studies.<sup>[35]</sup> Stressful life events are implicated in the emergence and persistence of gender differences associated with MDD,<sup>[35]</sup> postulating that women have a biological and/or psychological vulnerability towards developing an anxiety or mood disorder.<sup>[35]</sup> We have noted earlier that non-compliance and inappropriate discontinuation evokes a stress response that may adversely affect long-term outcomes.<sup>[21,22]</sup>

It could also be argued that males would be more likely to voluntarily discontinue their AD medication due to a stronger negative bias associated with the psychological stigma of the illness. However, we did not observe any significant association between compliance and gender. Two earlier studies have also noted that the gender of ambulatory patients treated with AD is a weak predictor of non-compliance.<sup>[18,36]</sup>

Our study also reveals that elderly patients (> 60 years) may be more compliant than younger populations taking ADs. In fact elderly patients demonstrate reduced dropout ratios and are more likely to comply with their medication, and in some cases respond better to treatment, than younger patients.<sup>[37]</sup> Younger patients have a stronger negative bias towards issues such as weight gain, sexual dysfunction and dissatisfaction with the physician.<sup>[38,39]</sup>

We also demonstrate that the treatment period has a definite influence on the MPR and patient compliance. We found that patients were prescribed an oversupply of AD during the first month of treatment. This is an interesting observation, especially since giving excessive medication may constitute a risk in patients with suicidal ideation. However, issues of dosage instability, side-effects and changing the regimen or dosage may explain this observation. Moreover, hospitalization and co-prescription of medicines may also occur. These findings should be considered when calculating MPR as a measure of patient compliance, taking into account that patients on AD treatment first need to be stabilized on the correct AD and dosage. However, it is of great concern that patients become gradually less compliant in the latter part of the four month treatment period.

The serotonin re-uptake inhibitors (SSRIs), represented here by escitalopram, citalopram, fluoxetine and sertraline, are first-line treatments for MDD due to improved safety and cost,<sup>[10]</sup> and are the most frequently dispensed class of ADs for this disorder.<sup>[40]</sup> Furthermore, their compliance in the SA private health sector amounts to between 32.8% and 35.4% (this study) which is slightly higher, when compared

to 25.5% reported elsewhere.<sup>[41]</sup> The low compliance with SSRIs in this study population is a noteworthy observation. We found compliance ratios for venlafaxine and duloxetine to be significantly better ( $p < 0.001$ ) (38.8% and 38.7%) than amitriptyline (26.2%). Amitriptyline displayed the worst compliance, perhaps because of its greater side effect burden.<sup>[42-44]</sup> A negative correlation was found between the initial PDD and the change in PDD, implying that the higher the initial PDD the smaller the change in PDD, particularly for venlafaxine, escitalopram, mirtazapine and amitriptyline. A higher initial PDD was also associated with better compliance to AD treatment. This finding is supported in the literature as several studies have found that MDD is commonly treated with inadequate doses of ADs.<sup>[45-47]</sup> Furthermore, another study by Marcus et al. (2009) found that a lower initial dose of AD was associated with subsequent switching to another AD or to an entirely new class of AD, suggesting that an inadequate dose at the start of treatment might contribute to a sub-optimal response to initial AD treatment and therefore increase the possibility of AD switching and relapse.<sup>[48]</sup>

## CONCLUSION

We established that compliance to AD treatment remains a major hindrance in the treatment of MDD in a middle-income developing country such as SA. These findings are worrisome as such non-compliance may have significant negative effects on the long-term treatment outcome of MDD but also of co-morbid disorders. Some of these aspects are currently under study by our research group. We found that only a third of patients suffering from MDD are compliant to their AD treatment, with newer generation ADs (particularly serotonin noradrenaline reuptake inhibitors (SNRI)) performing better. We also verified that data from medicine claims may be used as a measure of patient compliance in the clinical setting. Furthermore, the treatment period has a statistical significant effect on the MPR when used as a measure of compliance.

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## CHAPTER 3: MANUSCRIPT 3.3

In this chapter, a manuscript titled

“The impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private healthcare cohort”

is presented. The paper was submitted to the **AIDS Research and Therapy** as a full-length research report, and prepared according to the specific *Instructions to the Author* for this journal (provided in Addendum B). The references for this manuscript are provided at the end of this chapter.

This manuscript has been accepted for publication.

Instructions to the author can be viewed with the following link:

<http://www.aidsrestherapy.com/authors/instructions> Date of access: 19 Jun. 2014.

### 3.3 Article 3

#### **The impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private healthcare cohort**

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#### **ABSTRACT**

**Background:** MDD and HIV/AIDS have an extremely high prevalence worldwide with severe consequences for patients. In both conditions, compliance with treatment is key to successfully treat these disorders. In the current study, we examine the effect of MDD on the compliance with ADs in patients diagnosed with co-morbid HIV/AIDS and how different classes of ADs influence compliance in this group of patients.

**Methods:** A prospective, cohort study design was used to analyse nationally representative medicine claims data submitted to a privately-owned South African Pharmaceutical Benefit Management (PBM) company. Two groups were distinguished in the database, namely patients with only MDD and patients with both MDD and HIV/AIDS, over a six-year study period. The study population was determined by the following inclusion criteria: patients older than 18 years, MDD should be diagnosed by a psychiatrist supported by an appropriate ICD-10 code, and all patients have to be on combination antiretroviral treatment (cARV) treatment. The medicine possession ratio (MPR) was used as proxy to determine patient compliance with AD medication.

**Results:** 127 patients (i.e. 0.24%) met the criteria of co-morbid MDD and HIV/AIDS. Females have a significantly higher prevalence of MDD and HIV/AIDS when compared to males. Patients diagnosed with both HIV/AIDS and MDD (74.43. ± 32.03, 95%CI: 71.51-77.34) have a significantly lower compliance with AD treatment vs. MDD patients (80.94% ± 29.44, 95%CI: 80.56-81.33). In this group only 26.83% of TCA

had acceptable compliance compared to the 58.57% of SNRIs. Noteworthy observations were that 75% ( $p < 0.0217$ ; Cramer's  $V = 0.0388$ ) of venlafaxine and 28.6% ( $p < 0.0197$ ; Cramer's  $V = -0.0705$ ) of the paroxetine items were compliant in patients diagnosed with both HIV/AIDS and MDD.

**Conclusions:** AD compliance is lower in depressed HIV/AIDS vs. depressed non-HIV/AIDS patients. Venlafaxine might be considered as a first-line AD for MDD in HIV/AIDS patients, while anticholinergic antidepressants such as TCAs and paroxetine increase the risk of non-compliance. Prescribing ADs to females requires special consideration with respect to illness and treatment counselling to bring about improved compliance.

**Keywords:** Major depressive disorder, HIV/AIDS, compliance, antidepressants, Venlafaxine

## BACKGROUND

In 2012, the UNAIDS World AIDS Day Report estimated that approximately 34 million people worldwide are infected with human immunodeficiency virus (HIV), whereas 69% of these infected patients live in sub-Saharan Africa [1]. In the United States, more than one million individuals are infected with HIV and acquired immunodeficiency syndrome (AIDS, collectively HIV/AIDS), while nearly 50 000 more contract HIV each year [2]. In South Africa, the prevalence of HIV/AIDS is estimated to be 17.3% in the age group 15 to 49 years and approximately 5.6 million people in the country are living with HIV/AIDS [3]. South Africa is one of the countries with the highest HIV/AIDS-related mortality rates in the world, with approximately 270 000 deaths reported in 2011 [3].

Apart from the huge impact on the health system, HIV/AIDS also affects individual patients, causing a great deal of suffering in both their social lives as well as mental and physical health. It is therefore not surprising that HIV/AIDS is co-morbid with various psychosocial disorders, such as major depressive disorder (MDD) [4]. MDD is one of the main causes of psychiatric morbidity in HIV/AIDS patients [4]. In a six-month follow-up study in HIV/AIDS-infected patients in South Africa, Olley and co-workers described a 34.9% prevalence of MDD [5]. Elsewhere in the literature, however, there is some controversy over the prevalence of MDD in HIV/AIDS patients, with the prevalence rate varying between 3 and 54% [4, 6, 7]. Further studies in this regard are therefore urgently needed.

The co-morbidity between chronic illnesses and MDD is a well-recognised phenomenon. Chronically ill patients display two to three times higher rates of MDD when compared to healthy individuals of the same age and gender [8-10]. Diabetes, asthma, epilepsy, cancer, coronary heart disease, hypertension and HIV/AIDS are among the most common chronic illnesses that are associated with an increased prevalence of MDD [11, 12]. Considering the symptomatology of depression, depressed patients tend to neglect themselves due to fatigue, low energy levels, impaired memory and the sense of helplessness [13]. Patients with a chronic illness and co-morbid MDD have a significantly decreased compliance with self-care treatment regimens [14], which negatively affects long-term treatment outcomes and is ultimately associated with impaired daily functioning and a decreased quality of life [15, 16].

HIV-positive patients have twice the incidence of MDD compared to HIV-negative individuals [17-20]. In particular, late stage HIV (CD4 count of  $<200$  cells/ $\mu$ L) is associated with a significantly higher incidence of MDD, with a number of studies showing as much as a two and a half-fold increase in the incidence of MDD [21-24]. A recent study by Lopes and co-workers found that HIV-positive men were more likely to have a major depressive disorder/dysthymia (OR = 3.77; 95% CI, 1.16-12.27) when compared to HIV-negative males [25]. The reason for this is likely to be multifactorial, although chronic-psychosocial

stress (e.g. discrimination, isolation, violence, stigmatisation, hopelessness and drug abuse) [26] associated with HIV/AIDS can induce inflammation in the central nervous system (CNS), which is a major etiological factor [27]. Exposure to chronic psychosocial stress induces the continuous release of cortisol, and activates the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathetic autonomic nervous system, which in turn activates immune cells in both CNS and in the periphery [28, 29]. Depressed patients express elevated levels and an imbalance of cytokines, especially interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF  $\alpha$ ), which leads to cognitive and mood impairment [30-32]. Further evidence supporting inflammation as an etiological factor in depression, is that patients receiving interferon Alfa (IFN- $\alpha$ ) therapy for various types of cancer develop severe depression, INF being an inflammatory mediator [33-35]. Cerebral HIV infection will induce chronic inflammation in the brain and this causes the release of IFN and other cytokines, with depression as a result [27]. Therefore, HIV/AIDS patients with chronic increased cytokine levels as a result of viral infection, can be expected to be particularly vulnerable to develop depression [36].

The introduction of combination antiretroviral therapy (cART) has been successful in improving morbidity and decreasing the mortality rate of HIV/AIDS, which provides a glimmer of hope [37-39]. Importantly, however, cART can suppress HIV-1 RNA levels and increase CD4 T cell lymphocytes only if the cART is associated with excellent compliance and persistence [40-43]. Patients who are HIV positive must maintain a compliance rate of at least 95% in order to prevent virologic failure, increase CD4 T cell lymphocyte count, and decrease viral load and opportunistic infections [44-47]. Another risk associated with non-compliance with ART is the increased risk of viral resistance that ultimately leads to treatment failure [48-51]. On the other hand, compliance with AD treatment is just as important. Patients who fail to comply with their AD treatment have a twofold increased risk for relapse [52], are more likely to experience antidepressant withdrawal syndrome [53], and have a significantly increased mortality and morbidity rate associated with MDD [54]. Consequently, poor compliance with either ART or AD treatment will significantly compromise a successful treatment outcome.

The current literature regarding the prevalence of HIV/AIDS and MDD is quite limited. Therefore, this study will firstly strive to determine the prevalence of HIV/AIDS-positive patients within the MDD-diagnosed population in the private health sector of South Africa. Secondly, the study will investigate how AD compliance is affected by MDD in HIV/AIDS-positive patients when compared to depressed non-HIV/AIDS patients and, lastly, whether AD compliance has any association with gender and antidepressant class in this population.

## **RESULTS**

The research cohort consisted of two groups, namely MDD patients with HIV/AIDS (n = 127) and patients with only MDD (n = 12 270).

Table 1: Patient demographics

Total number of patients in the study						
Illness	n	%				
MDD + HIV	127	0.24				
MDD	12270	22.94				
HIV	41086	76.82				

Gender classification of the study population						
Illness	Male			Female		
	n	%		n	%	
MDD + HIV	37	29.13		90	70.87	
MDD	3496	28.49		8774	71.51	
HIV	18268	44.46		22818	55.54	

Age classification of the study population						
Illness	> 18 ≤ 40 years		>40 ≤ 60 years		>60 years	
	n	%	n	%	n	%
MDD + HIV	31	24.41	75	59.06	21	16.54
MDD	2662	21.7	21176	47.03	3837	31.27
HIV	16586	40.37	21176	51.54	1652	4.02

The mean MPR of antidepressants (ADs) was significantly lower ( $p < 0.0001$ ;  $d = 0.2255$ ) in MDD patients with HIV/AIDS ( $74.43\% \pm 32.03$ , 95%CI: 71.51-77.34) than in patients with only MDD ( $80.94\% \pm 29.44$ , 95%CI: 80.56-81.33). In MDD patients with HIV/AIDS, antidepressant compliance (MPR) was significantly lower in females ( $69.35\% \pm 29.69$ , 95%CI: 66.03-72.67) than in males ( $84.51\% \pm 34.18$ , 95%CI: 79.10-89.91) from the same cohort ( $p < 0.0001$ ;  $d = 0.4755$ ). Age was not a significant predictor of AD compliance in MDD patients with HIV/AIDS ( $p < 0.9519$ ) and those with only MDD ( $p = 0.1111$ ), as shown in Table 2.

Table 2: The effect of illness, gender and age on medicine possession ratio (MPR)

Mean MPR in MDD patients with/without HIV/AIDS (dispensed items)					
Illness	n	Mean ± SD (%)	95%CI	p*	Cohen's d-value
HIV/AIDS + MDD	466	74.43 ± 32.03	71.51-77.34	0.0001	0.2255
MDD	22831	80.94 ± 29.44	80.56-81.33		

\* Two-sample t-test

Mean MPR in MDD patients with HIV/AIDS vs. Gender (dispensed items).					
Gender	n	Mean ± SD (%)	95%CI	p*	Cohen's d-value
Female	310	69.35 ± 29.69	66.03-72.67	0.0001	0.4755
Male	156	84.51 ± 34.18	79.10-89.91		

\* Two-sample t-test

Mean MPR in MDD patients without HIV/AIDS vs. Gender (dispensed items)				
Gender	n	Mean ± SD (%)	95%CI	p*
Female	16600	80.97 ± 29.72	80.52-81.43	0.8067
Male	6231	80.87 ± 28.65	80.16-81.58	

\* Two-sample t-test

Mean MPR in MDD patients with HIV/AIDS vs. Age group (dispensed items)				
Age (Years)	n	Mean ± SD (%)	95%CI	p**
> 18 ≤ 40	126	74.57 ± 32.39	68.86-80.29	0.9519
> 40 ≤ 60	284	74.61 ± 33.07	70.74-78.47	
> 60	56	73.16 ± 25.74	66.27-80.06.	

\*\* One-way ANOVA

Mean MPR in MDD patients without HIV/AIDS vs. Age group (dispensed items)				
Age (Years)	n	Mean ± SD (%)	95%CI	p**
> 18 ≤ 40	4320	81.39 ± 28.89	80.56-82.28	0.1111
> 40 ≤ 60	10929	80.52 ± 29.85	79.96-81.08	
> 60	7582	81.30 ± 29.15	80.65-81.92	

\*\* One-way ANOVA

In Table 3, a significant association was found between AD class and AD compliance in MDD patients with HIV/AIDS, with compliance figures as follows; tricyclic antidepressants (TCA) 26.83%; selective serotonin re-uptake inhibitors (SSRIs) 44.93%; diverse antidepressants 52.70%; and serotonin and noradrenalin re-uptake inhibitors (SNRIs) 58.57% ( $p < 0.0001$ ; Cramer's  $V = 0.3450$ ).

Table 3: The influence of AD class on AD compliance in MDD patients with/without HIV/AIDS (dispensed items)

<b>MDD patients with HIV/AIDS (dispensed items)</b>					
<b>Antidepressant class</b>	<b>n</b>	<b>Acceptable (%)</b>	<b>Unacceptable (%)</b>	<b><i>p</i>***</b>	<b>Cramer's <i>V</i></b>
SSRIs	207	44.93	55.07	< 0.0001	0.3450
Diverse antidepressants	148	52.70	37.30		
SNRIs	70	58.57	41.43		
TCA	41	26.83	73.17		
<b>MDD patients without HIV/AIDS (dispensed items)</b>					
<b>Antidepressant class</b>	<b>n</b>	<b>Acceptable (%)</b>	<b>Unacceptable (%)</b>	<b><i>p</i>***</b>	<b>Cramer's <i>V</i></b>
SSRIs	9435	51.64	48.36	0.0001	0.0942
SNRIs	5777	56.36	43.64		
Diverse antidepressants	5460	48.24	51.76		
TCA	2159	43.72	56.28		

\*\*\* Chi-square

The following ADs, as depicted in Table 4, were associated with unacceptably low levels of compliance in MDD patients with HIV/AIDS vs. patients with only MDD, as observed from the compliance ratio: amitriptyline 23.53% vs. 39.34% ( $p < 0.0618$ ; Cramer's  $V = -0.0494$ ); trazodone 27.27% vs. 50.72% ( $p < -0.0239$ ; Cramer's  $V = -0.0630$ ); paroxetine 28.57% vs. 54.19% ( $p < 0.0197$ ; Cramer's  $V = -0.0705$ ); duloxetine 36.67% vs. 55.51% ( $p < 0.0391$ ; Cramer's  $V = -0.0426$ ); escitalopram 44.16% vs. 52.74% ( $p < 0.0359$ ; Cramer's  $V = -0.0254$ ); bupropion 78.26% vs. 50.46% ( $p < 0.0082$ ; Cramer's  $V = 0.0698$ ) and venlafaxine 75.00% vs. 56.93% ( $p < 0.0217$ ; Cramer's  $V = 0.0388$ ).

Table 4: Percentage of the top 10 most frequently dispensed antidepressants with acceptable vs. non-acceptable compliance in MDD patients with/without HIV/AIDS (dispensed items)

	HIV+MDD				MDD				<i>p</i> ***	Cramer's <i>V</i>
	n	Acceptable	n	Unacceptable	n	Acceptable	n	Unacceptable		
Mirtazapine	40	51.28	38	48.72	848	46.41	979	53.59	0.3987	0.0193
Escitalopram	34	44.16	43	55.84	1781	52.74	1596	47.26	0.1359	-0.0254
Venlafaxine	30	75.00	10	25.00	1972	56.93	1492	43.07	0.0217	0.0388
Citalopram	25	51.02	18	48.92	1002	51.46	945	48.54	0.9511	-0.0014
Fluoxetine	19	41.30	25	58.70	724	47.95	786	52.05	0.3743	-0.0225
Bupropion	18	78.26	5	21.74	714	50.46	701	49.54	0.0082	0.0698
Duloxetine	11	36.67	19	63.33	1284	55.51	1029	44.49	0.0391	-0.0426
Amitriptyline	8	23.53	26	76.47	548	39.34	845	60.66	0.0618	-0.0494
Trazodone	6	27.27	16	72.73	596	50.72	579	49.28	0.0293	-0.0630
Paroxetine	6	28.57	15	71.43	582	54.19	492	45.81	0.0197	-0.0705

\*\*\* Chi-square

## DISCUSSION

This study focused on the prevalence of HIV/AIDS-positive patients within the MDD-diagnosed population in this section of the private health sector of South Africa. Secondly, the study investigated how AD compliance is affected by MDD in HIV/AIDS-positive patients when compared to depressed non-HIV/AIDS patients, and whether AD compliance has any correlation with gender and antidepressant class in this population. These goals were attained in that we were able to confirm the co-morbidity between MDD and HIV/AIDS-positive patients; however, due to the strict inclusion criteria, the numbers of patients were small, which provided a limited picture of the overall prevalence between MDD and HIV/AIDS-positive patients.

This study found that patients diagnosed with both HIV/AIDS and MDD ( $74.43 \pm 32.03$ , 95%CI: 71.51-77.34) have a significantly lower compliance with AD treatment when compared to patients diagnosed only with MDD ( $80.94\% \pm 29.44$ , 95%CI: 80.56-81.33). The current study confirms that patients suffering from both MDD and HIV/AIDS have a decreased compliance with MDD treatment. This trend is confirmed in the literature as several authors have found similar results, namely that patients suffering from both conditions are less compliant to AD treatment regimens [14, 20, 55, 56]. Our data also seem to suggest, in Table 4, that patients with HIV/AIDS are less compliant with ADs that present with multi-receptor pharmacology, i.e. TCAs (26.83% compliance; Table 3) and paroxetine (compliance 28.57%, Table 4), while they are more compliant with pharmacologically 'clean' ADs, such as the venlafaxine (75% compliance, Table 4). The TCAs display a high binding affinity for non-specific receptors such as muscarinic (mACh), histaminic (HA-1) and alpha-1 adrenoceptors, which are responsible for side effects such as dry mouth, constipation and sedation [57]. Similarly, paroxetine demonstrates an affinity for mACh receptors similar to that of imipramine and has marked anticholinergic adverse effects [57]. Our data infer that the reduced compliance with these antidepressants may have a biological basis, in particular an apparent increase in cholinergic sensitivity in the HIV/AIDS population. Indeed, cholinomimetic antibodies of the immunoglobulin (IgA) class are present in HIV/AIDS patients [58, 59], suggesting that these patients may indeed be hypersensitive to drugs with activity on the cholinergic system [60]. Importantly, TCA and paroxetine non-compliance with TCAs and paroxetine can evoke a cholinergic overdrive [57, 61], which may augment the hyper-cholinergic state present in HIV/AIDS patients, leading to a greater adverse experience and subsequent non-compliance. Furthermore, since MDD is associated with increased cholinergic drive [62, 63], it is clear that poor compliance in this population may worsen the mood disorder. For the successful treatment of both MDD and HIV/AIDS, compliance with treatment is therefore of utmost importance. Poor compliance with treatment can lead to a drastic decline in quality of life, increased social impairment, low occupational functioning and heightened social isolation, increased suicide ideation and ultimately to suicide [21, 55, 56, 64-66].

Another interesting result is that the class of antidepressant plays a significant role in predicting compliance when treating patients with MDD and HIV/AIDS. The tricyclic antidepressant (TCA) class is associated with the weakest compliance ratio (26.83%), whereas the SNRIs present with the highest compliance ratio (58.57%). According to our results, SSRIs represent the class of ADs with the highest prescription frequency (44.42%, N = 466). Both escitalopram and citalopram are considered as first-line treatment for treating MDD in HIV/AIDS patients because of a limited effect on the cytochrome P450 system, thereby reducing drug-drug interactions with ARV treatment [67-69]. Moreover, a number of studies have proposed that MDD associated with HIV/AIDS should be treated with fluoxetine and paroxetine [70-72]. However, their use is limited by drug-drug interaction with protease inhibitors (PIs) due to their potent inhibition of CYP2D6, thereby increasing levels of PIs and associated toxicity [57, 67,

73]. However, in this study, the SSRIs as a group displayed a relatively weak compliance ratio (44.93%;  $p < 0.0001$ ; Table 3) compared to the SNRIs, which displayed a significantly higher compliance ratio (58.57%;  $p < 0.0001$ ; Table 3). These findings indicate that the SSRIs have more adverse effects in this population than originally predicted, possibly related to their anticholinergic (paroxetine), antihistaminic (citalopram) and general serotonergic properties [57]. In fact, considering the latter point, neuropsychiatric symptoms may be evident in HIV-treated patients, especially those on efavirenz, and respond to treatment with the antiserotonergic agent, cyproheptadine, suggesting increased serotonergic activity/sensitivity in these patients [74]. Furthermore, inappropriate AD discontinuation and non-compliance are also associated with increased serotonergic activity [75] that may amplify the adverse experience associated with HIV/AIDS-related neurotransmitter dysregulation. What is more important considering our data is that SNRIs are currently considered a second-line treatment for MDD in HIV/AIDS patients [68, 69], while our data (preliminary as they may be) suggest a possible re-evaluation of these guidelines. Indeed, further studies in this regard are warranted.

Only 127 patients (i.e. 0.24% of the total population in the database) met the criteria of co-morbid MDD and HIV/AIDS. Currently, there exists great controversy in the literature regarding the co-morbidity between depression and HIV/AIDS, with a number of articles placing the co-morbidity rate between 0 and 54% [4, 6, 7, 55]. This finding again highlights the complicated co-morbidity between MDD and HIV/AIDS, the different approaches, methodology and reporting of results used in several studies with regard to the selection of a study population, the demographics and the behaviour of the defined population. Furthermore, the low prevalence rate found in this study might suggest a severe under diagnoses of MDD in HIV/AIDS patients and that MDD symptoms might be mistaken rather as symptoms of HIV/AIDS [76, 77].

We also observed that female patients ( $n = 90$ ) were more than double that of male patients ( $n = 37$ ). Female patients diagnosed with both MDD and HIV/AIDS displayed significantly lower compliance with AD treatment when compared to male patients of the same group, and displayed almost double the prevalence of both MDD and HIV/AIDS than male counterparts. Some of the reasons given for the poor compliance rate to AD treatment in women are the risk of adverse effects (e.g. weight gain and sexual dysfunction), low socio-economic status, younger age, drug abuse and divorce marital status [78]. Similar to our findings, two separate studies found that almost double the number of women with MDD and HIV/AIDS are likely to die from an HIV/AIDS-related cause when compared to HIV-positive women without depression [79], while females have a significantly higher frequency of MDD and HIV/AIDS vs. males with a combined diagnosis [80, 81]. Some authors have suggested that lower levels of testosterone might play a role in the large prevalence of MDD in females when compared to men [82]. In support of this, males with hypogonadism have a significantly higher prevalence of MDD and anxiety disorders when compared to healthy males [83, 84]. Moreover, testosterone-replacement therapy in hypogonadal men significantly improves these symptoms [83, 85, 86]. Importantly, studies have found benefits in administering testosterone to depressed women [87, 88], thereby supporting the role of testosterone as a causal factor for MDD in women. However, a study in depressed HIV/AIDS patients has shown that testosterone displayed no significant effect on mood [56].

Examining individual ADs dispensed to patients who are suffering from both MDD and HIV/AIDS, mirtazapine was the most frequently dispensed AD ( $n = 78$ ), followed closely by escitalopram ( $n = 77$ ). Although mirtazapine is not a first-line AD for the treatment of MDD, its side effect profile seems to play a valuable role in late-stage HIV/AIDS patients with co-morbid MDD, with side effects such as

constipation, weight gain and sedation helping to improve diarrhoea, diminished appetite and insomnia, respectively [67].

The strength of the current study is that only patients diagnosed with MDD by a psychiatrist were included in the study population. This article has shed light on the current practice of AD treatment in HIV/AIDS patients with medical aids. The most important findings include that HIV/AIDS with co-morbid MDD have reduced compliance with ADs, especially those exhibiting multi-receptor pharmacology, most notably TCAs and certain SSRIs such as paroxetine. Secondly, MDD patients with co-morbid HIV/AIDS display significantly higher compliance with venlafaxine, contrary to current clinical practice where guidelines suggest SSRIs and SNRIs as first and second line treatment options, respectively. Further clarification with respect to duloxetine is needed as it performed poorly in our analysis. Lastly, female patients are more prone to develop MDD and are notably less compliant with AD treatment.

The authors recognise a few limitations in the current study. Firstly, the numbers of patients with both MDD and HIV/AIDS were relatively small and not a full representation of the national population. Several factors contributed to the small sample size, such as the use of very strict inclusion criteria, only a portion of all the medical aids is listed with the PBM utilised in this study, depressed patients using psychological treatment for MDD were not taken into account, while the study population consisted of only patients contributing to a private medical aid/insurance. Secondly, the use of a database limits the further extraction of patient information regarding the stage of HIV/AIDS in which the patient is and whether there was an improvement or deterioration in the patient's mood.

## **CONCLUSION**

This study confirms that AD compliance is lower in depressed HIV/AIDS vs. depressed non-HIV/AIDS patients, correlating with global trends regarding non-compliance of patients with a chronic disease and co-morbid disorders. Moreover, the fact that the prevalence of MDD patients with co-morbid HIV/AIDS was limited in this study again highlights the need for more research in various population groups with a focus on the socio-economic status of the patients. Although our data are preliminary and warrant further study, it does reveal evidence that venlafaxine may be a valid choice of antidepressant in HIV/AIDS patients suffering from MDD and should be considered as first-line antidepressant in such cases. Moreover, our data suggest that multi-target antidepressants such as TCAs and select SSRIs may increase the risk of non-compliance in this population. Lastly, when prescribing ADs to females, special consideration should be given to counselling them on both their illness and treatment so that they clearly understand the benefits of compliance to treatment.

## **METHODS**

We conducted a prospective, cohort study analysing nationally representative medicine claims data submitted to a privately-owned South African Pharmaceutical Benefit Management (PBM) company. The data represent a third of South African patients with private medical aids. No distinction was made between races. Two groups were distinguished in the database over a six-year study period (1 January 2006 to 31 December 2011), namely patients with only MDD (n = 12 270) and MDD patients with HIV/AIDS (n = 127).

We queried data for patient demographics (gender and date of birth) and pertinent prescription information (such as drug trade name, days supplied, dispensing date, quantity of medicine prescribed, and ICD-10 code per claim). The following automated validation processes were applied by the PBM

that ascertained the quality of data: data integrity validation, eligibility management, medicine utilisation and clinical management, pricing and formulary management. There were no missing data fields in the datasets. The variables 'birth date' and 'dispensing date' were used to calculate the age of patients on the date of treatment and the number of days between refills.

A study population was selected according the following inclusion criteria: patients older than 18 years, MDD should be diagnosed by a psychiatrist supported by an appropriate ICD-10 code. The ICD-10 codes are based on the International Classification of Diseases, 10<sup>th</sup> edition published by the World Health Organization [89]. In this study, the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist, as well as B20-B24 (Human immunodeficiency virus [HIV/AIDS] disease), and all patients on cARV treatment. Thereby it was ensured that data were excluded where ADs may have been used for other indications, such as amitriptyline for the treatment of chronic pain.

For the purpose of this study, the medicine possession ratio (MPR) was used to determine AD compliance of patients. The MPR is a well-established method to calculate drug compliance in pharmacoepidemiological studies, including chronic diseases such as MDD [90], hypertension [91], and schizophrenia [92]. However, it is important to note that the compliance value obtained from the MPR only gives an indication of the possession of medicine by the patient, and that appropriate consumption of medicine is assumed to ensue from possession. The usage of medicine claims data to determine MPR calculations is valuable in that it is acceptably accurate, convenient, objective, non-invasive and relatively inexpensive to obtain when a large study population is needed. It is therefore suitable for the calculation of MPR as an indication of patient compliance with medication therapy [93, 94]. However, the MPR has a number of limitations. Firstly, MPR can only be calculated if a patient has filled more than two prescriptions. Secondly, MPR can only assess whether the medication was used consistently. Lastly, the MPR cannot measure whether a patient was compliant with the instructions given by the medical practitioner [95].

The MPR is defined as the number of days for which medication is supplied within the refill interval (medicine treatment period) divided by the number of days in the refill interval [96, 97].

$$\text{MPR} = \frac{\text{Number of days in refill interval}}{\text{Sum the days of supplied medication}} \times 100$$

The MPR is considered acceptable if the calculated value is  $\geq 80\%$ , but  $\leq 110\%$ . An MPR of less than 80% indicates the presence of refill gaps so that possession is considered unacceptably low (undersupply), whereas an MPR greater than 110% is considered unacceptably high (oversupply). Conversely, a patient was considered compliant (acceptable group) with his/her AD treatment if the MPR was  $\geq 80\%$  and  $\leq 110\%$ , and AD treatment period was longer than 120 days. Therefore, distinguishing between compliant MPR group and patients out of this range will be considered as the non-compliant MPR group or unacceptable group.

Data management and analysis were performed in SAS Version 9.1.3 (SAS Institute, Cary, NC) [98]. All statistical significance was considered with a probability of  $p < 0.05$ . The practical significance of results was computed when the  $p$ -value was statistically significant ( $p \leq 0.05$ ).

Variables (age groups, gender and active ingredients) were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations and 95% confidence intervals (CI). The

patient's age was determined at time of first dispensing and divided into three groups: > 18 to ≤ 40 years; > 40 to ≤ 60 years; > 60 years. .

The dataset is very large, therefore all the statistical methods used in this study rely on the Central Limit Theorem, which states that the average of a large number of independent random variables is approximately normally distributed around the true population mean [99]. Therefore, the two-sample t-test allowed us to compare the mean MPR of male and female patients. The one-way ANOVA was used to test differences between the mean MPR of different age groups and AD classes. It was operationalised with the general linear model (GLM) procedure of the SAS Version 9.1.3. If a difference was indicated, a Tukey's multiple comparison test was performed to determine which groups differ significantly from each other. Cohen's d was used to evaluate effect size between means (with  $d \geq 0.8$  defined as a large effect with practical significance). The Chi-square test ( $\chi^2$ ) was used to determine whether an association exists between proportions of two or more groups (compliance vs. active ingredients). The Cramer's V statistic was used to test the practical significance of this association (with Cramer's  $V \geq 0.5$  defined as practical significance).

This study was approved by the Research Ethics Committee of the North-West University (NWU-0046-08-550) and the Board of Directors of the South African Pharmaceutical Benefit Management (PBM). Data were analysed anonymously.

#### **AUTHORS' CONTRIBUTIONS**

FN Slabbert has been involved in the design of the study, drafted the manuscript, and carried out the analyses and interpretation of data. MS Lubbe made a substantial contribution in the design of the study and developed the methodology. BH Harvey and CB Brink revised the manuscript and have given extensive intellectual inputs. All authors read and approved the final manuscript.

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## CHAPTER 3: MANUSCRIPT 3.4

In this chapter, a manuscript titled

“The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort”

is presented. This paper is included as a concept article in the current research thesis. This article was prepared according to the requirements of the journal **BMC Psychiatry** as a full-length research report.

Instructions to the author can be viewed with the following link:

<http://www.biomedcentral.com/bmcpsychiatry/authors/instructions> Date of access: 15 Sep. 2014.

### 3.4 Article 3.4

#### **The influence of co-prescribed GABA-ergic drugs on antidepressant compliance in patients with depression: A prospective study in a South African private healthcare cohort**

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#### **Abstract**

**Background:** Despite the progress made in recent years regarding our understanding of the neurobiology of major depressive disorder (MDD), approximately one third of patients remain unresponsive to treatment. Co-prescribing of GABA-ergic drugs (GDs), such as sedative hypnotics, with antidepressants (ADs) is not uncommon, although how they benefit the outcome, if at all, remains controversial. Adequate compliance is central to a positive outcome, although its impact with respect to drug usage patterns has not been considered. The aim of the current study is to establish how the co-prescribing of GDs is associated with altered antidepressant compliance and which antidepressants (ADs) are associated with the worst compliance in combination with GDs.

**Methods:** A prospective, cohort study design was used to analyse nationally representative medicine claims data submitted to a privately-owned South African Pharmaceutical Benefit Management (PBM) company. Three groups were distinguished over a six-year study period, namely patients treated only with ADs, those treated only with GDs and those treated with both ADs and GDs. The study population was determined by means of the following inclusion criteria: AD and/or GDs prescribed, patients older than 18 years, and MDD diagnosed by a psychiatrist supported by an appropriate ICD-10 code. The medicine possession ratio (MPR) was used as proxy to determine patient compliance for both AD and GD medication.

**Results:** The overall AD compliance of patients taking both ADs and GDs (35.19% acceptable compliance; n = 42 869) was weak, and no statistically significant difference ( $p = 0.0657$ ) was observed compared to patients taking only ADs (35.44% acceptable compliance; n = 8 247). The lowest percentage of patients taking amitriptyline (29.57%), mirtazapine (31.36%) and fluoxetine (32.29%) in addition with GDs were

associated with compliance, with a higher percentage of duloxetine (40.67%), venlafaxine (38.62%), and citalopram (38.50%) that were compliant. ADs with the highest non-compliance were associated with a significant increase in GDs prescribing.

**Conclusion:** The addition of GDs does not increase AD compliance. The class of AD is *not* always a risk factor for non-compliance. Different ADs show differences with respect to GD co-prescribing, which may be related to side effect burden and patient acceptability. Non-compliance and associated use of GD may correlate with ADS.

**Keywords:** major depressive disorder, compliance, medicine possession ratio, treatment resistant depression, GABA-ergic drugs, co-prescribing, long-term outcome

## **Background**

In the last two decades, significant progress has been made in our understanding of the underlying neurobiology of major depressive disorder (MDD) [1-3], although this progress has not realised a likewise increase in new drug development with improved outcomes. In fact, current drugs are no more effective than treatments developed six decades ago [4], with only a third of depressed patients on antidepressant (AD) treatment attaining remission [5, 6]. Moreover, high dropout rates due to unwanted side effects [7] and poor overall compliance, with 45 to 60% of patients stopping their AD treatment within the first three months of treatment [8, 9], further complicate matters [3].

Failure to respond to AD treatment and achieving remission have severe consequences on patients, which include increased social and functional impairment, higher risk for recurrence and relapse of a depressive episode, a weak treatment prognosis, significant increase in treatment cost, over-utilisation of healthcare systems, and ultimately an increase in the risk of suicide [10-12]. Poor response, psychosocial stigma and non-compliance, in turn, lead to complications such as the AD discontinuation syndrome (ADS) and treatment resistance, both of which can severely compromise the long-term outcome [9].

The complex nature of MDD, particularly the variable presence of a number of symptoms as well as comorbid disorders related to sleep and anxiety often necessitates the need for the co-prescribing of other classes of psychotropic together with the AD [13]. Moreover, side effects associated with some ADs, such as anxiety and insomnia with SSRIs, also often prompt co-prescribing [14].

Drugs acting on  $\gamma$ -amino-butyric acid (GABA) signalling, otherwise referred to as GABA-ergics drugs (GDs) (e.g. benzodiazepines, zolpidem and zopiclone), are currently the most widely prescribed psychotropic drugs world-wide [13]. The comorbidity between anxiety disorders and depression is approximately 50 to 60% [15-17], making the co-prescribing of ADs in combination with anxiolytics and sedative hypnotics fairly common [18]. Although there is the perception that such prescribing should benefit the treatment of MDD, clinical trials have found benzodiazepines to have a limited effect on the treatment of MDD, as they only address the agitation, insomnia and anxiety associated with MDD [19]. However, benzodiazepines are closely associated with adverse effects such as dependence, discontinuation withdrawal and impaired cognition that ultimately limit their efficacy [18]. These clinical detractors have discouraged the use of benzodiazepines in the treatment of MDD, and as stipulated by international guidelines [20-22]. The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Disorders (CANMAT) recommend the use SSRIs and SNRIs as the first-line treatments for anxiety associated with MDD [20]. Furthermore, the American Psychiatric Association (APA)

recommends that the use of benzodiazepines should be limited and that benzodiazepine should not be used as a first-line option in the treatment of anxiety, especially in patients with severe MDD [22]. Moreover, recent studies have suggested that GABA mimetic sedative hypnotics may be detrimental or counter-productive to AD treatment outcomes. A pre-clinical study by Wu and Castrén suggested that the co-administration of diazepam with fluoxetine abrogates the effects of fluoxetine on crucial sub-cellular processes related to AD action [23]. In the clinical scenario, the chronic use of benzodiazepines has been found to aggravate depression and even increase the risk of suicide [24, 25]. In contrast, benzodiazepines are suggested to be advantageous during the initial treatment phase (two to four weeks) of MDD as it has a faster onset of action and therefore reduces anxiety-related symptoms associated with both MDD and AD induced anxiogenic effects [14, 19, 26, 27]. Importantly, benzodiazepines have been found to increase AD treatment compliance during the first weeks of treatment compared to patients taking ADs alone and to reduce dropout rates; however, after six to twelve weeks, benzodiazepine's effects on AD treatment dropout diminished significantly [28].

Within the benzodiazepine class, there are differences in terms of potency, onset of action and half-life [26]. Clonazepam and diazepam are proven to be as effective an anxiolytic as alprazolam, the latter also being the only benzodiazepine that is claimed to have antidepressant-like effects [29-31]. Lorazepam and other benzodiazepine associated with short a half-life (lormetazepam, oxazepam and temazepam) are not recommended as anxiolytics in MDD patients, due to their increased risk for dependency [20, 32]

Another class of sedative hypnotics include the non-benzodiazepine group of GABA-ergic drugs, such as zolpidem and zopiclone. Zolpidem and zopiclone are currently some of the most widely dispensed sedative hypnotics [13] and are frequently co-prescribed with ADs for the treatment of insomnia associated with MDD [18]. However, the overuse of these drugs is associated with marked cognitive impairment and dementia, which could take up to six months to improve after the discontinuation of these drugs [33].

There is much disagreement regarding the treatment period for MDD. Long-term trials are utilised to study the long-term effectiveness of AD treatment [34], thereby demonstrating efficacy in maintenance treatment. In an eight-year follow-up study, Colman and co-workers found that patients who started AD treatment during the initial depressive episode had a better long-term prognosis, while other studies [35, 36] found that a longer depressive episode before the initiation of AD treatment was associated with a worse long-term outcome. Furthermore, the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study found that more treatment steps needed to achieve remission resulted in lower overall remission rates [6]. Therefore, AD treatment alone may not always be adequate and in some instances may even be counter-productive [9]. This phenomenon has been referred to as oppositional tolerance, whereby depressive illness can become refractory through either switching ADs or applying augmentation strategies [37, 38].

The main aim of the current study is to determine the influence of co-prescribed GDs on AD treatment compliance. Furthermore, this study will investigate the GDs additionally prescribed to MDD patients. As well as determine which ADs are associated with the worst compliance in combination with GDs and whether there is a relationship between AD treatment compliance and the use of GDs. A prospective analysis (1 January 2006 to 31 December 2011) will be carried out using patients from the private health sector in South Africa.

## Methods

We conducted a prospective, cohort study analysing nationally representative medicine claims data submitted to a privately-owned South African Pharmaceutical Benefit Management (PBM) company. The data represent a third of patients with private medical insurance in South Africa. Three patient groups were distinguished in the database over a six-year study period (1 January 2006 to 31 December 2011), namely patients receiving only AD treatment ( $n = 4255$ ), patients receiving only GDs ( $n = 269689$ ) and the last group consists of patients who received both AD and GDs ( $n = 8142$ ).

We obtained data for patient demographics (date of birth) and pertinent prescription information (such as drug trade name, days supplied, dispensing date, quantity of medicine prescribed, and ICD-10 code per claim). Several automated validation processes were applied by the PBM to ensure the quality of data. There were no missing data fields in the datasets. The variables 'birth date' and 'dispensing date' were used to calculate the age of patients on the date of treatment and the number of days between refills.

All patients included in this study were older than 18 years of age and were diagnosed with MDD by a psychiatrist supported by the correct ICD-10 code based upon the International Classification of Diseases, 10<sup>th</sup> edition published by the World Health Organization [39]. In this study, the ICD-10 codes F32 (Depressive episode) and F33 (Recurrent depressive disorder) were used to identify patients with MDD as diagnosed by a psychiatrist. The GDs are commonly co-prescribed with ADs with possible benefits [40], although only GDs specifically linked to the treatment of anxiety and insomnia were included in this study (see Table 5). The inclusion criteria for the GDs are based on the South African Monthly Index of Medical Specialties (MIMS) classification [41].

The medicine possession rate (MPR) is a well-established method of calculating drug compliance in pharmacoepidemiological studies, including chronic diseases such as depression [42], hypertension [43], osteoporosis [44] and schizophrenia [45]. However, it is important to note that the compliance value obtained from the MPR only provides an indication of the possession of medicine by the patient, and that appropriate consumption of medicine is assumed to ensue from possession. The usage of medicine claims data to determine the MPR is useful in that it is acceptably accurate, convenient, objective, non-invasive and relatively inexpensive to obtain when a large study population is needed. It is therefore suitable for the calculation of MPR as an indication of patient compliance with medication therapy.

For the purpose of this study, the MPR and the medicine treatment period were used to determine AD and GDs compliance of patients. In order to treat MDD effectively and to prevent relapse, patients must be on chronic AD treatment for at least 120 days or more. Therefore, all patients on ADs with a  $MPR \leq 80\%$  or  $MPR \geq 110\%$  and/or an AD treatment period  $< 120$  days were deemed non-compliant. All patients on GDs with an  $MPR \leq 80\%$  or  $MPR \geq 110\%$  were deemed non-compliant. Conversely, a patient was considered compliant with his/her AD treatment if:

- MPR was  $\geq 80\%$  and  $\leq 110\%$ , and
- AD treatment period was longer than 120 days.

Data management and analysis were performed in SAS Version 9.1.3 (SAS Institute, Cary, NC) [46]. All statistical significance was considered with probability of  $p < 0.05$ . The practical significance of results (see Tables 2 and 3 using the Cramer's  $V$  and Cohen's  $d$ -value) was computed when the  $p$ -value was statistically significant ( $p \leq 0.05$ ).

Variables (treatment period and active ingredients) were expressed using descriptive statistics such as frequencies ( $n$ ), percentages (%), means, and 95% confidence intervals (CI). Treatment duration for an AD was calculated as the time (in days) from the date of the first prescription until the date of the last prescription.

Chi-square test ( $\chi^2$ ) was used to determine whether an association exists between proportions of two or more groups (diagnoses vs. MPR groups). The Cramer's  $V$  statistic was used to test the practical significance of this association (with Cramer's  $V \geq 0.5$  defined as practically significant). The two-sample  $t$ -test allowed us to determine whether the AD treatment period differs statistically significantly between the AD complaint and AD non-complaint group of patients who received both AD and GDs. The Cohen's  $d$  value was used to evaluate the effect size between means (with  $d \geq 0.8$  defined as practically significant).

This study was approved by the Research Ethics Committee of the North-West University (NWU-0046-08-A5) and the board of directors of the South African Pharmaceutical Benefit Management (PBM). Data were analysed anonymously.

### **Results and discussion**

Table 1 summarises the demography of the cohort, which consisted of three different groups, namely patients receiving only AD treatment ( $n = 4255$ ), patients receiving only GDs ( $n = 269689$ ), and patients receiving both an AD and a GD ( $n = 8142$ ).

Table 1: Total number of patients in the study

	n	%
AD	4255	1.51
AD + GD	8142	2.89
GD	269 689	95.61

AD = Antidepressant, GD = GABA-ergic drug

The prevalence of AD and GD compliance is depicted in Table 2. No statistically significant association ( $p = 0.657$ ) was found between the compliance to AD treatment with (AD + GDs 35.19% acceptable compliance;  $n = 42869$ ) or without (AD 35.44% acceptable compliance;  $n = 8247$ ) additional GD treatment. AD treatment had a statistically significant ( $p < 0.0001$ ) effect on the compliance of GD treatment regimens (GD 22.47% acceptable compliance;  $n = 529433$  and GD + AD 25.03% acceptable compliance;  $n = 42869$ ).

Table 2: The effect of GABA-ergic drugs on antidepressant compliance and the effect of antidepressants on GABA-ergic compliance (items dispensed)

	n	Acceptable compliance (%)	Unacceptable compliance (%)	$p$ value*	Cramer's $V$
ADs compliance without/with GDs					
AD	8247	35.44	64.56	0.6570	-0.0020
AD + GD	42 869	35.19	64.81		
GD compliance without/with AD treatment					
GD	529 433	22.47	77.53	< 0.0001	0.0161
GD + AD	42 869	25.03	74.97		

AD = Antidepressant, GD = GABA-ergic drug.

\* Chi-square test

In Table 3, the most frequently dispensed ADs in combination with GDs are listed. The 11 ADs listed in Table 3 constitute approximately 90% of all dispensed ADs. Amitriptyline was associated with the worst treatment compliance, with only 24.30% and 29.57% of patients being compliant alone and in combination with GDs, respectively. Mirtazapine (AD 30.18% vs. AD + GD 31.36%) and fluoxetine (AD 33.38% vs. AD + GD 32.29%) have second and third lowest levels of compliance when co-prescribed with GDs. The four drugs with the best compliance when prescribed without GDs (duloxetine, venlafaxine, citalopram and escitalopram) remained associated with the best levels of compliance in combination with GDs (respectively 40.67%, 38.62%, 38.50% and 37.43%). Although not indicated in the table, a statistically significant ( $p < 0.05$ ) difference was found between the different AD classes in patients on both ADs and GDs; duloxetine (40.67%) vs. amitriptyline (29.57%), venlafaxine (38.62%) vs. amitriptyline (29.57%) and escitalopram (37.43%) vs. mirtazapine (31.36%). Venlafaxine was the most frequently (13.93%,  $n = 5936$ ) dispensed AD in combination with a GD.

Table 3: Antidepressant compliance rates associated with antidepressant treatment alone vs. antidepressant treatment plus GABA-ergic drug treatment

	Number of prescriptions			AD co-prescribed with GD (%)	Acceptable compliance (%)		Comparison AD versus AD + GD	
	Total	AD	AD + GD		AD	AD + GD	<i>p</i> value*	Cramer's <i>V</i>
DULOXETINE	4 568	698	3 870	84.72	37.53	40.67	0.12	0.02
VENLAFAXINE	7 118	1182	5 936	83.39	43.23	38.62	0.12	0.11
CITALOPRAM	4 042	758	3 284	81.25	37.86	38.50	0.75	0.01
ESCITALOPRAM	7 007	1487	5 520	78.78	35.31	37.43	0.13	0.02
PAROXETINE	2 585	385	2 200	85.11	34.03	34.86	0.39	0.02
SERTRALINE	2 936	598	2 338	79.63	31.27	34.64	0.12	0.03
BUPROPION	2 785	626	2 159	77.52	33.07	34.46	0.52	0.01
TRAZODONE	2 765	318	2 447	88.50	35.22	34.16	0.71	-0.01
FLUOXETINE	4 016	662	3 354	83.52	33.38	32.29	0.60	-0.01
MIRTAZAPINE	4 716	507	4 209	89.25	30.18	31.36	0.60	0.01
AMITRIPTYLINE	3 648	358	3 290	90.19	24.30	29.57	0.04	0.03

AD = Antidepressant, GD = GABA-ergic drug.

\* Chi-square t

In Table 4, we investigated the differences in the AD treatment period of AD patients on GABA-ergic drugs with acceptable vs. unacceptable AD compliance. A statistically significant ( $p < 0.0001$ ) difference was found between the mean AD treatment period (in days) (406.55; 95%CI: 403.20 - 409.90 vs. 252.68; 95%CI: 250.20 - 255.20) of all AD compliant vs. AD non-compliant groups, indicating that acceptable compliance was closely associated with a prolonged treatment period. Furthermore, 90% of amitriptyline and 89% of mirtazapine containing products were co-prescribed with a GD.

Table 4: Differences in the AD treatment period of AD patients on GABA-ergic drugs with acceptable vs. unacceptable AD compliance

	Mean treatment period (days)				Comparison acceptable versus unacceptable compliance	
	Acceptable compliance		Unacceptable compliance		<i>p</i> value*	<i>d</i> value**
	Mean	95% CI	Mean	95%CI		
DULOXETINE	354.31	346.71 - 361.90	232.33	224.74 - 239.92	< 0.0001	0.48
VENLAFAXINE	379.90	371.94 - 387.86	256.31	249.13 - 263.48	< 0.0001	0.38
CITALOPRAM	460.90	447.30 - 474.50	297.38	285.49 - 309.26	< 0.0001	0.42
ESCITALOPRAM	388.31	379.92 - 396.68	238.11	231.47 - 244.74	< 0.0001	0.52
PAROXETINE	356.49	344.13 - 368.86	210.33	199.47 - 221.20	< 0.0001	0.52
SERTRALINE	429.34	414.66 - 444.01	253.28	241.82 - 264.75	< 0.0001	0.49
BUPROPION	436.78	422.91 - 450.64	242.18	232.81 - 251.55	< 0.0001	0.70
TRAZODONE	462.96	445.47 - 480.45	256.44	245.84 - 267.04	< 0.0001	0.55
FLUOXETINE	451.41	438.29 - 464.53	262.49	254.47 - 270.51	< 0.0001	0.53
MIRTAZAPINE	404.41	394.33 - 414.49	227.23	220.41 - 234.03	< 0.0001	0.59
AMITRIPTYLINE	392.30	372.20 - 412.30	276.90	263.3 - 290.60	< 0.0001	0.41
<b>All ADs</b>	<b>406.60</b>	<b>403.20 - 409.90</b>	<b>252.70</b>	<b>250.20 - 255.20</b>	<b>&lt; 0.0001</b>	<b>0.47</b>

AD = Antidepressant

\* Student's t-test

\*\* Cohen's *d*-value

Table 5 is a summary of the most frequently dispensed GDs in combination with ADs. Alprazolam was the most frequently dispensed GD. Zopiclone was associated with the highest level of compliance (acceptable compliance = 31.40%; n = 6125) when co-prescribed with ADs. In Table 5, AD treatment was found to significantly ( $p < 0.0001$ ) increase GD compliance (zopiclone (28.54% vs. 31.40%), alprazolam (22.92% vs. 25.11%) and diazepam (7.26% vs. 17.85%)), but decreased the compliance of lorazepam (23.94% vs. 17.67%) statistically significantly.

Table 5: GABA-ergic drug compliance without/with AD treatment (items dispensed)

	Total n <sup>#</sup>	Acceptable Compliance				Comparison acceptable versus unacceptable compliance	
		GD		GD + AD		p value	Cramer's V
		n <sup>##</sup>	(%)	n <sup>###</sup>	(%)		
ZOPICLONE	80 649	74 524	28.54	6 125	31.40	< 0.0001	0.0173
OXAZEPAM	23 921	22 599	28.81	1 322	29.05	0.851	0.0012
TEMAZEPAM	10 683	9 905	27.80	778	28.41	0.7158	0.0037
ZOLPIDEM	141 610	132 298	25.15	9 312	25.43	0.5548	0.0016
ALPRAZOLAM	125 699	115 498	22.92	10 201	25.11	< 0.0001	0.0147
MIDAZOLAM	10 402	9 795	17.19	607	22.24	0.0015	0.0321
BROMAZEPAM	44 950	42 969	21.08	1 981	21.86	0.4101	0.0040
CLOBAZAM	28 210	25 504	17.95	2 706	19.62	0.033	0.0133
DIAZEPAM	31 320	29 928	7.26	1 392	17.82	< 0.0001	0.0831
LOPRAZOLAM	24 779	22 487	23.94	2 292	17.67	< 0.0001	-0.0448

AD = Antidepressant, GD = GABA-ergic drug

<sup>#</sup> Total number of dispensed GDs without/with AD treatment

<sup>##</sup> Number of GDs dispensed without AD treatment

<sup>###</sup> Number of GDs + AD treatment

The main findings of this study are that the overall compliance with both AD and GDs separately and together is poor (combined acceptable compliance = 35.19%). Amitriptyline, mirtazapine and surprisingly fluoxetine were associated with the lowest compliance rate. Importantly, the longer the AD treatment period in the AD plus GD group, the more acceptable the AD treatment compliance was. Furthermore, the ADs associated with the weakest compliance (amitriptyline and mirtazapine) were associated with the highest prevalence of co-prescribing of GDs based on the percentage of GDs co-prescribed with AD treatment (Table 3).

The current study found a significant association between acceptable compliance and a prolonged treatment period for ADs. Although only 35.19% of ADs used by patients displayed acceptable, the combined (ADs + GDs) group was associated with a significantly ( $p < 0.0001$ ) longer AD treatment period when compared to the non-compliant group (406.55 days; 95%CI: 403.20 - 409.90 vs. 252.68; 95%CI: 250.20 - 255.20). This result is in line with Hotopf *et al.* (1997), who found that up to 30% of patients stop taking AD treatment in the first 30 days and between 45 and 60% of patients discontinue their AD treatment within the first three months [8]. Moreover, in 2013, the World Federation of Societies of Biological Psychiatry (WFSBP) published international guidelines regarding the AD treatment period [47]. This document states that MDD patients should be treated for 12 weeks during the acute treatment phase, then six to nine months on the continuation phase. Lastly, if a patient is in remission, treatment should be continued for six to 24 months in the maintenance phase [47]. Therefore, the findings described in our study concur with international guidelines that non-compliance is an inevitable consequence of AD treatment and that discontinuation will most likely occur within the first year of treatment. However, in the current study, we were not able to determine exactly when GDs were prescribed. Therefore, we weren't able to confirm acute vs. chronic use of the GDs, the latter being more associated with a negative outcome in MDD [14, 19, 26, 27].

Non-compliance was found to be high in the current study; as much as 64% of patients with/without the addition of a GD did not meet the criteria for acceptable AD compliance. There are various reasons for non-compliance with AD treatment, including that patients discontinue treatment when they start to feel better, the stigma attached to mental illness, forgetting to take AD treatment, price of medication, thinking they will become better without ADs, fear of drug dependency and the occurrence of adverse effects [9, 48]. Whatever the reason, inappropriate AD discontinuation is associated with an increased risk of relapse, recurrence and suicide [49]. Furthermore, antidepressant discontinuation syndrome (ADS) is also closely associated with non-compliant behaviour (see review Harvey & Slabbert, 2014) [9] that may also adversely affect long-term outcomes.

Amitriptyline, mirtazapine and fluoxetine were associated with the weakest compliance rates. Amitriptyline is associated with anticholinergic side effects such as a dry mouth, constipation, sexual dysfunction, blurred vision and urinary retention [50], while mirtazapine is known to cause sedation and weight gain [51], which may explain the poor compliance noted with these two agents. However, SSRIs are generally regarded as being better tolerated than most ADs [52], and therefore the high non-compliance rate of fluoxetine is surprising. Importantly, it may suggest another reason over and above side effects for the observed non-compliance with this agent. On the other hand, serotonergic side effects with SSRIs and SNRIs are increasingly being viewed as problematic for adherence, especially issues related to sexual dysfunction, weight gain, and cognitive and emotional blunting [9]. Although it would be presumptuous to assume this to be an exclusive problem with fluoxetine, other studies have found that the AD effect of fluoxetine diminishes over time, with patients having a relapse rate of 26% (48% for placebo) after 24 weeks, but decreasing to 11% (16% = placebo) at week 62 [53]. Such a decrease in AD effect might prompt prescribers to use an augmentation strategy, either by increasing the dosage [54], adding a GD drug [55] or switching the patient to a new AD [56], all of which may compromise compliance associated with fluoxetine. Further analyses aimed at delineating the presence of prior AD discontinuations as well as determining any association of such behaviour with a poorer outcome are needed.

We found that combining GDs drugs with AD treatment had no noticeable influence on the AD compliance of MDD patients (Table 2) (AD + GDs drugs 35.19% vs. AD 35.44%). Important to note is that some of the key symptoms of the ADS are anxiety/agitation, irritability, nightmares and sleep disturbances [9], which may explain this tendency to co-prescribe these agents. Although historically these drugs have been used especially in the early stages of treatment to address anxiety and insomnia in MDD [20, 21], current international guidelines discourage the use of benzodiazepines as they do not have any antidepressant effects [20-22]. Interestingly, alprazolam which has some antidepressant effects [31], was the most frequently dispensed GD. Moreover, some studies suggest that GABA mimetics counter the therapeutic effects of an AD [23]. One of the criteria for this study was that a patient needed to use an AD for longer than 120 days, which aligns with previous findings that the chronic utilisation of anxiolytics and sedative hypnotics does not benefit AD treatment and compliance. Due to issues related to their dependence-producing properties as well as retarding AD response noted earlier, they may further complicate the treatment of MDD.

We found that ADs with the highest non-compliance (amitriptyline, mirtazapine and fluoxetine) were associated with an increased prescribing of GDs drugs. This phenomenon may arise as a direct consequence of the adverse effects profiles of these drugs leading to early discontinuation and poor compliance. That 90% of amitriptyline and 89% of mirtazapine containing products were co-prescribed with a GD is of interest, especially since both these ADs have profound sedative hypnotic effects of their

own, so why co-prescribe a GD? We feel such co-prescribing has *nothing* to do with wanting to introduce a sedative hypnotic per se, but more to address the behavioural consequences of AD discontinuation. Indeed, ADS is well known to illicit symptoms relating to anxiety, agitation, insomnia, nightmares etc. [9] that will explain the increased co-prescribing of GDs in this population. Venlafaxine, on the other hand, is the most compliant AD (43.23%) yet also was the most frequently dispensed AD in combination with a GD. This paradox may be due to the activating profile of this AD, often necessitating co-prescribing of a GD to counter symptoms relating to agitation and anxiety [57]. The association of fluoxetine with GD co-prescribing is less clear, especially since ADS is less likely with this SSRI due to its long-half-life [57]. However, like venlafaxine, fluoxetine is regarded as an activating SSRI [57], which may more explain its co-prescribing with a GD.

## **CONCLUSION**

In the current study, the overall compliance with AD treatment was weak, while the addition of GD drugs did not markedly improve compliance. Furthermore, we found that ADs (amitriptyline, mirtazapine and fluoxetine) with the highest non-compliance were associated with an increased prescribing of GD drugs and, contrary to clinical opinion, class of AD is not always a risk measure for non-compliance.

Different ADs show differences with respect to GD co-prescribing, which may be related to side effect burden and acceptability to the patient. Non-compliance and associated use of GD may therefore correlate with ADS, although further studies are needed to separate acute vs chronic GD use in this population.

Lastly, using a prospective analysis of medicine claims data, we were able to access the level of non-compliance within the South African context.

## **AUTHORS' CONTRIBUTIONS**

FN Slabbert was involved in designing the study, drafted the manuscript, carried out the analyses and interpretation of data. MS Lubbe made a substantial contribution to the design of the study and developed the methodology. BH Harvey and CB Brink revised the manuscript and provided extensive intellectual inputs. All authors read and approved the final manuscript.

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## CHAPTER 4: CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS

In this chapter, the conclusions and key findings of the current study will be discussed, recommendations regarding future studies will be provided and the limitations of the current study will be underscored in order to improve follow-up studies.

### 4.1 Conclusions and key findings deduced from the literature review

#### 4.1.1 New insights into antidepressant discontinuation syndrome

In this section, the most salient findings of the review article will be discussed.

##### 4.1.1.1 Proposed neurobiology underlying ADS

AD non-compliance is an established obstacle in the treatment of MDD. Failure to respond to AD treatment and achieving remission has severe neurobiological and clinical consequences. The clinical consequences include increased social and functional impairment, higher risk of recurrence and relapse of a depressive episode, a weak treatment outcome, significant increase in treatment cost, over-utilisation of healthcare systems, and ultimately an increased suicide risk (Trivedi *et al.*, 2008; Dunner *et al.*, 2006; Carney & Freedland, 2009). However, the neurobiological consequences are much more far reaching. One of the more serious yet under-recognised neurobiological complications of AD non-compliance is the development of ADS, which is the result of non-compliance or the abrupt discontinuation of AD treatment (Warner *et al.*, 2006; Narayan & Haddad, 2010). Antidepressant discontinuation syndrome (ADS) is closely associated with most of the current ADs used to treat MDD, and includes TCAs, SRIs, SNRIs as well as atypical compounds (Haddad & Anderson, 2007; Narayan & Haddad, 2010). Although the experimental data regarding the neurobiology and pharmacologic mechanisms underlying ADS are limited, both clinical and pre-clinical studies have found that inappropriate AD discontinuation provokes a bio-behavioural stress response that, in an already vulnerable individual, can have devastating effects on treatment response and illness prognosis (Overstreet & Wegener, 2013; Harvey *et al.*, 2003). Furthermore, disturbances in glutamate function are suggested to play a significant role in the development of ADS (Harvey *et al.*, 2002; Harvey *et al.*, 2003), while increased glutamate transmission following stress is recognised as one of the key causal elements of depression (Harvey, 2008; Wegener *et al.*, 2010; Gao & Bao, 2011). Since the discontinuation of an AD promotes a stress response in both rats (Harvey *et al.*, 2002) and humans (Michelson *et al.*, 2000), AD discontinuation may very likely increase glutamate release and the activation of a number of excitotoxic mechanisms (Karreman & Moghaddam, 1996; Timmerman *et al.*, 1999). The subsequent activation of, for example, the nitrergic pathway seems to be serotonin-dependent and plays an important role in neuroplasticity and cell survival (Harvey *et al.*, 2006). These sub-cellular processes may underlie the association between repeated AD discontinuation, increasing structural brain changes, and eventually treatment failure (Harvey *et al.*, 2003). Additionally, we have suggested that irregular 5-HT release is a primary mediator of ADS, especially via actions on SERT, 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors (Harvey & Slabbert, 2014). Furthermore, the aforementioned hyperserotonergia may be counter-productive to a successful outcome, possibly leading to undesirable neurotransmitter and neuroplasticity changes that negatively affect resilience and recovery (Vaidya *et al.*, 1999). Based on previous animal work in our laboratory (Harvey *et al.*, 2002; 2006) and the critical review paper undertaken as part of the outcomes for this study (Harvey & Slabbert, 2014), we propose that the

neurobiology of ADS resides in AD discontinuation induced imbalances in serotonin, either hyposerotonergia or hyperserotonergia, that is an inherent property of all currently available ADs, bar one.

#### **4.1.1.2 Agomelatine vs. serotonergic ADs in the treatment of MDD**

Agomelatine is one of the most recent classes of ADs that does not directly influence monoamine transmission (De Bodinat *et al.*, 2010), acting as an agonist at melatonergic MT1 and MT2 receptor and as a neutral antagonist at 5-HT<sub>2C</sub> receptors (Fornaro *et al.*, 2010; Demyttenaere, 2011; Guardiola-Lemaitre *et al.*, 2014). The antidepressant activity of agomelatine is reliant on the synergy between the aforementioned receptor effects, particularly in the SCN (Racagni *et al.*, 2011). Agomelatine can bind directly to 5-HT<sub>2C</sub>/MT receptors in the brain or indirectly target the SCN where it presumably modifies glutamate output from the SCN (Abrahamson & Moore, 2001), which affects DA, NA and 5-HT cell bodies in the brain stem (Chenu *et al.*, 2013; McClung, 2013). One of the main distinctions found between agomelatine and current ADs (TCAs, SRIs and SNRIs) is that it does not increase synaptic 5-HT during acute treatment, but only after chronic dosing (Chenu *et al.*, 2013). Furthermore, agomelatine does not induce ADS after abrupt discontinuation, which we argue in our review (Harvey & Slabbert, 2014) is one of its most under-recognised benefits. In this review, we present startling evidence in support of the role of 5-HT in ADS and how currently used ADs target 5HT in a non-physiological manner, ADS being closely linked to the release of 5-HT by the AD and ensuring long-term effects on 5-HT<sub>1A/2C</sub> receptors, SERT and MAO density (Harvey & Slabbert, 2014). Lastly, agomelatine's pharmacokinetics further defy the rules when compared to traditional ADs. Agomelatine has a T<sub>1/2</sub> of only 2.5 hours, which is significantly shorter than other ADs that normally would place it at high risk for the development of ADS. The ability of agomelatine to enhance 5-HT levels indirectly over a prolonged period without inducing overt serotonergic effects has introduced a new train of thoughts in the treatment of MDD that not only will be beneficial for patients, but may herald new ideas in AD drug design where minimising serotonergic activity takes preference. This will reduce adverse effects, enhance treatment compliance and improve the overall outcome, as well as limit long-term neurobiological sequel in the event of inappropriate discontinuation.

## **4.2 Conclusions deduced from the empirical investigation**

The following conclusions can be made from the last three research manuscripts (Chapter 3.2-3.4):

### **4.2.1 Prospective analysis of the medicine possession rate (MPR) of antidepressants in the private health sector of South Africa (2006 to 2011)**

#### **4.2.1.1 Establishing non-compliance as a hurdle in AD treatment**

One of the key challenges preventing the successful treatment of MDD is poor AD treatment compliance (Osterberg & Blaschke, 2005; Keller & Boland, 1998). The term treatment compliance implies much more than simply taking one's medication correctly. Non-compliance manifests in several ways, such as a patient taking only some of the prescribed medication, taking a lower dosage than prescribed, missing or skipping doses, delaying to take the prescribed AD(s), taking drug holidays, and patients who are fully compliant with their pharmacological treatment regimens, but fail to comply with other therapeutic interventions (Colom *et al.*, 2005; Demyttenaere *et al.*, 2001). Furthermore, the current study establishes that approximately 66% of patients in a private health sector who received AD treatment are non-compliant. This finding concurs with what other studies have reported, viz. that between 30 and

60% of patients do not comply with AD treatment (Cramer, 1995; Demyttenaere, 1997). Therefore, the current research confirmed that AD treatment non-compliance remains a major hindrance in the successful treatment of MDD and that it is an existing complication in the private healthcare setting in South Africa.

#### **4.2.1.2 The association between gender and AD treatment compliance**

Gender was found to be a predictor of AD treatment non-compliance in this study. The current study found that female patients suffering from MDD were more than double that of male patients. Females were also found to be significantly more non-compliant with AD treatment when compared to male patients. In the literature, several reasons have been put forward to explain this occurrence, which include that women are more at risk/sensitive for developing adverse effects (e.g. weight gain and sexual dysfunction) (Demyttenaere, 1997). Some authors have suggested that lower levels of testosterone might also play a role in the large prevalence of MDD in females when compared to men (McHenry *et al.*, 2014). In support of this, males with hypogonadism have a significantly higher prevalence of MDD and anxiety disorders when compared to healthy males (DiBlasio *et al.*, 2008; Zarrouf *et al.*, 2009). Moreover, testosterone-replacement therapy in hypogonadal men significantly improves these symptoms (Pope *et al.*, 2003; Wang *et al.*, 1996; Zarrouf *et al.*, 2009). Importantly, studies have found benefits in administering testosterone to depressed women (Miller *et al.*, 2009; Shifren *et al.*, 2000), thereby supporting the role of testosterone as a causal factor of MDD in women. Therefore, based on the literature and the current findings described in this thesis, special consideration should be given when initiating AD treatment in female patients with the focus on efficient counselling on both their illness and treatment so that they clearly understand the benefits of compliance with treatment.

#### **4.2.1.3 The influence of change in PDD on AD compliance**

An inadequate dosage is associated with treatment non-compliance during the initial treatment phase (Marcus *et al.*, 2009). In order to successfully treat MDD, it is therefore of utmost importance that a patient is started on an adequate dosage. The European Group for the study of Resistant Depression (GSRD) has operationalised the term 'adequate dosage', the dosage to be as high as the lowest recommended dosage for the treatment of MDD according to the datasheet of the drug (Schosser *et al.*, 2012). Furthermore, the current study found a negative correlation between the initial PDD and the change in PDD, meaning that a higher initial AD dosage was associated with a smaller change in dosage over the treatment period. Another finding of interest is that a higher initial dosage was associated with improved AD treatment compliance. The importance of an adequate treatment dosage cannot be overstated, since unsuccessful AD treatment during the initial treatment phase means failure to achieve remission. This scenario will, in turn, complicate matters in an already stressed and fragile individual, possibly resulting in ADS due to the stopping and starting of an AD thereby increasing the risk of treatment resistance and ultimately increasing suicide risk.

#### **4.2.1.4 Influence of AD class in AD treatment compliance**

The current research found that certain ADs were more associated with treatment non-compliance than others. Amitriptyline was associated with the greatest incidence of non-compliance, with the probable reason for this being its more severe adverse effect profile (Baldwin, 2001; Hirschfeld, 2000; Masand, 2003). The most common side effects associated with amitriptyline are anticholinergic in nature, including dry mouth, constipation, sexual dysfunction, blurred vision and urinary retention (Harvey,

1997). On the other hand, citalopram and escitalopram were associated with improved compliance rate in this study. Both these ADs are considered to be first-line treatments for MDD due to improved safety, tolerability and cost (Gelenberg *et al.*, 2010). Therefore, an unfavourable side effect profile will negatively affect the success of a given AD treatment regimen. Therefore, clinicians should consider the adverse effects associated with each AD as well as the individual patient as some patients are more sensitive to certain side effects than others are. However, even ADs within the same class may differ with respect to side effects; this being due to differences in pharmacological profiles (Harvey, 1997). Therefore, paroxetine has a subtly different side effect profile compared to other SSRIs due to its more pronounced anticholinergic properties (Harvey, 1997).

#### **4.2.1.5 The influence of gender on MDD and AD treatment compliance**

This study found the prevalence of MDD in female patients to be almost double that of males, and in keeping with previous studies (Kessler, 2003). Stressful life events are implicated in the emergence and persistence of gender differences associated with MDD, (Kessler, 2003) postulating that women have a biological and/or psychological vulnerability towards developing an anxiety or mood disorder (Kessler, 2003). We have noted earlier that non-compliance and inappropriate discontinuation evokes a stress response that may adversely affect long-term outcomes (Harvey *et al.*, 2003; Harvey, 2006).

It could also be argued that males would be more likely to voluntarily discontinue their AD medication due to a stronger negative bias associated with the psychological stigma of the illness. However, we did not observe any significant association between compliance and gender. Two earlier studies have also noted that the gender of ambulatory patients treated with AD is a weak predictor of non-compliance (Lin *et al.*, 1995; Simon *et al.*, 1993).

#### **4.2.1.6 The influence of age on AD treatment compliance**

In the current research thesis we established that elderly patients (> 60 years) may be more compliant than younger populations taking ADs. In fact elderly patients demonstrate reduced dropout ratios and are more likely to comply with their medication, and in some cases respond better to treatment, than younger patients (Birrer & Vemuri, 2004). Younger patients have a stronger negative bias towards issues such as weight gain, sexual dysfunction and dissatisfaction with the physician (Akincigil *et al.*, 2007; Tamburrino *et al.*, 2009).

### **4.2.2 Impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private health care cohort**

#### **4.2.2.1 HIV/AIDS and AD treatment compliance**

In South Africa, an estimated 5.6 million people are living with HIV/AIDS (WHO, 2011), many of whom suffer from an anxiety or mood disorder such as MDD (Olley *et al.*, 2006). However, no studies have considered the extent of co-morbidity between HIV/AIDS and MDD in a South African population, which consequently became a central outcome of this study. We also investigated how the presence of an HIV/AIDS diagnosis influences AD treatment compliance in MDD patients. As described in other studies (Chandler *et al.*, 2006; DiMatteo *et al.*, 2000; Rabkin, 2008; Sin & DiMatteo, 2014), we confirmed that the presence of HIV/AIDS reduces AD treatment compliance.

Furthermore, patients with HIV/AIDS are especially less compliant with ADs that present with multi-receptor pharmacology, i.e. amitriptyline and paroxetine, while they are more compliant with

pharmacologically 'clean' ADs, such as venlafaxine. Interesting enough, although venlafaxine is not considered to be a first choice AD in this population, we found it to be associated with the highest rate of compliance in HIV/AIDS patients. Moreover, our data infer that reduced compliance with these antidepressants may have a biological basis, in particular an apparent increase in cholinergic sensitivity in the HIV/AIDS population. Indeed, cholinomimetic antibodies of the immunoglobulin (IgA) class are present in HIV/AIDS patients (Borda *et al.*, 1993; de Bracco *et al.*, 1993), suggesting that these patients may indeed be hyper-sensitive to drugs with activity on the cholinergic system (Sales *et al.*, 1997). Importantly, non-compliance with TCAs and paroxetine can evoke a cholinergic overdrive (Harvey, 1997; Harvey *et al.*, 2003) that may augment the hyper-cholinergic state present in HIV/AIDS patients, leading to a greater adverse experience and subsequent non-compliance.

Furthermore, since MDD is associated with an increased cholinergic drive (Furey *et al.*, 2010; Mineur *et al.*, 2013), poor compliance in this population may worsen the mood disorder. For the successful treatment of both MDD and HIV/AIDS, compliance with treatment is therefore of the utmost importance. In patients with co-morbid illnesses (not only limited to HIV/AIDS), it is very important to adjust and prescribe AD treatment according to a particular individual's needs in order to promote treatment compliance for both conditions.

#### **4.2.3 The influence of co-prescribed GABAergic drugs on antidepressant compliance in patients with depression. A prospective study in a South African private health care cohort**

##### **4.2.3.1 The development of TRD might be a possible consequence of non-compliance**

In a study by Souery *et al.* (1999), it was estimated that approximately 20% of all TRD cases are a direct consequence of AD non-compliance (Souery *et al.*, 1999). When taking the neurobiological alterations and the manifestation of ADS, caused by treatment non-compliance, into account, this observation is not surprising after all. Therefore, based on the results from the current study (acceptable compliance = 35.19%) and the evidence in the literature, AD non-compliance might not only significantly compromise long-term treatment outcome, but might also be a precursor (or present as an adverse environmental condition) that will prompt the development of TRD. These results emphasise the importance of AD compliance.

##### **4.2.3.2 The relevance of AD class and AD treatment compliance**

Amitriptyline, mirtazapine and fluoxetine were associated with the weakest compliance rates. Amitriptyline is associated with anticholinergic side effects such as a dry mouth, constipation, sexual dysfunction, blurred vision and urinary retention (American Psychiatric Association, 2010), while mirtazapine is known to cause sedation and weight gain (Ciraulo *et al.*, 2011) that may explain the poor compliance noted with these two agents. However SSRIs are generally regarded as being better tolerated than most ADs (Bet *et al.*, 2013) and therefore the high non-compliance rate of fluoxetine is surprising. Importantly, it may suggest another reason over and above side effects for the observed non-compliance with this agent. On the other hand, serotonergic side effects with SSRIs and SNRI's is increasingly being viewed as problematic for adherence, especially issues related to sexual dysfunction, weight gain, and cognitive and emotional blunting (Harvey & Slabbert., 2014). Although it would be presumptuous to assume this to be an exclusive problem with fluoxetine, other studies have found that the AD effect of fluoxetine diminishes over time, with patients having a relapse rate of 26% (48% for placebo) after 24 weeks, but decreasing to 11% (16% = placebo) at week 62 (Reimherr *et al.*, 1998). Such a decrease in AD effect might prompt prescribers to use an augmentation strategy, either by

increasing the dosage (Schmidt *et al.*, 2002), adding a GDs drug (Blier *et al.*, 2010) or switching the patient to a new AD (Poirier & Boyer, 1999), all of which may compromise compliance associated with fluoxetine. Further analysis aimed at delineating the presence of prior AD discontinuations as well as determining any association of such behaviour with a poorer outcome is needed.

#### **4.2.3.3 The relationship between AD treatment period, non-compliance and a possible risk of compromising long-term outcome**

In 2013, the World Federation of Societies of Biological Psychiatry (WFSBP) published international guidelines regarding the AD treatment period (Bauer *et al.*, 2013). This document states that patients should be treated for 12 weeks during the acute treatment phase, then six to nine months on the continuation phase, and lastly, if a patient is in remission, treatment should be continued for six to 24 months in the maintenance phase (Bauer *et al.*, 2013). Therefore, the findings described in our study concur with international guidelines that long-term treatment (and by implication acceptable compliance) results in a better treatment prognosis.

#### **4.2.3.4 The influence of co-prescribed GABAergic drugs on AD compliance**

We also investigated the relationship between AD compliance and the co-prescribing of various GABAergic drugs, particularly sedative hypnotics and the anxiolytics which are used to treat anxiety associated with MDD. GABAergic drugs were found to cause a slight decrease in the compliance with AD treatment, although it was not of statistical significance. This is an interesting observation, since the rationale for adding GDs is to reduce symptoms, to enhance AD compliance and to enhance treatment response. Considering class of AD, this study noted that class is *not* always a risk factor for non-compliance, since ADs such as the TCA, amitriptyline, which is known to have a high side effect profile, and the SSRI, fluoxetine, had the same level of non-compliance, while other SSRIs, such as escitalopram, were markedly better. Furthermore, we found that ADs with the highest non-compliance were associated with increased prescribing of GDs, which may hint at a possible association with the ADS or even TRD (although further study in this regard is required). As previously noted in our review article (Harvey & Slabbert, 2014), the key symptoms associated with ADS include sleep disturbances, nightmares, anxiety/agitation and irritability. This suggests that, due to poor overall treatment compliance, the majority of patients might experience some of the symptoms commonly associated with ADS, which may prompt the prescribing of BZDs to counter these symptoms. Such prescribing is of concern, especially since co-prescribing of a benzodiazepine has been found to decrease AD activity (Wu & Castren, 2009), while current treatment guidelines discourage the use of BZDs in MDD patients due to the risk of dependence and that they do not possess robust antidepressant activity (American Psychiatric Association, 2010; Baldwin *et al.*, 2011; Kennedy *et al.*, 2009). In summary, the co-prescribing of GDs did not improve AD compliance. The high usage of sedative hypnotics is indicative of an associated increase in ADS symptomology, and for which BZDs are often prescribed. The observed co-prescribing of these drugs with ADs may decrease the efficacy of AD as well as negatively affecting treatment by introducing the complication of BZD dependence; starting and maintaining a vicious cycle that may further complicate prognosis, e.g. possibly introducing TRD.

In final conclusion, the study has identified and confirmed a number of factors that may have a negative effect on AD treatment compliance:

- The chronic co-prescribing of BZDs might influence chronic AD treatment negatively.

- Inappropriate initial dosage.
- Gender was found to be strong predictor for non-compliance; therefore special consideration should be given before prescribing just any AD.
- The choice of AD plays a vital role in non-compliance.
- Co-morbid illnesses, in this study HIV/AIDS, can profoundly affect compliance with an AD.
- Venlafaxine should be considered as first-line choice in MDD patients with co-morbid HIV/AIDS.
- Patients with HIV are more sensitive to cholinergic side effects and therefore more prone to non-compliance with ADs with anticholinergic properties.
- ADs (amitriptyline, mirtazapine and fluoxetine) with the highest unacceptable compliance were associated with increased prescribing of GDs, which might be indicative of ADS.
- Prolonged AD treatment was associated with increased compliance.
- AD treatment non-compliance is as big an obstacle in developing countries as in developed countries.
- With the initiation of AD treatment it is of utmost importance that a patient is started on an adequate dosage.

Except for the risk for the development of ADS, taking the literature into account, treatment non-compliance could be considered a major risk, if not a precursor for the development of later complications in treatment, such as TRD. Based on the findings of this work, and using a unique study design and method, we have confirmed that AD treatment non-compliance is and remains a major hindrance in the effective management of MDD in the private healthcare sector in South Africa, specifically patients belonging to a medical aid.

Our critical review of the literature around the ADS and its relationship to pharmacology also revealed novel ideas pertaining to the underlying neurobiology of ADS and how this may adversely affect the long-term outcome. This review also suggested new strategies of relevance to drug research and development to enable better designed drugs for the treatment of MDD.

### **4.3 Recommendations for future studies**

Suggestions for future research therefore include:

- Evidence to date suggests that agomelatine is not associated with the development of ADS and does not possess any serotonergic side effects, it would be of interest to investigate whether agomelatine is also associated with improved long-term outcome and a lower incidence of TRD vs serotonergic ADs. At the time of the study, agomelatine had only recently been launched in South Africa, and therefore no retrospective data on this drug were available on the PBM database.
- Research is needed to determine whether agomelatine's superior clinical profile regarding ADS may be linked to improved compliance over time as well as improved long-term outcome.

- The hypotheses proposed regarding the underlying neurobiology of ADS need extensive pre-clinical and clinical testing.
- There is an urgent need to establish a validated and reliable animal model for ADS in order to study the development of ADS and its neurobiological correlates.
- The co-morbidity between MDD and HIV/AIDS must be determined in a larger cohort. It is also recommended to study this co-morbidity in the public sector of South Africa as government has an extensive HIV/AIDS treatment campaign.
- The current study focused only on the private health sector using medical claims data. It is recommended that research on populations that do not have the benefit of a medical aid be undertaken in order to assess the impact of socio-economic status on compliance.
- The current finding that venlafaxine might be a valid first-line choice in MDD patients with co-morbid HIV/AIDS warrants further research, as venlafaxine is currently not considered an AD of choice for the treatment of MDD co-morbid with HIV/AIDS.
- The current study established that AD non-compliance is a major obstacle in the treatment of MDD. However, further in-depth studies using an appropriate study design are recommended in order to establish a possible link between AD treatment non-compliance and the development of TRD. Therefore, based on the current findings, we recommend a future study that will focus on the development of TRD by identifying appropriate therapeutic markers in the PBM data indicative of TRD, such as augmentation strategies, an escalation in dosage and switching between AD classes, as assessed during the initial treatment phase and followed up over time thereafter. Then, analyse co-prescribed psychotropic drugs (as indicated by the international treatment guidelines for TRD) in this group of individuals to improve the sensitivity of the study method in determining the prevalence of TRD.

#### **4.4 Limitations of the current study**

The next section will provide a brief summary of the limitations of the current study.

- A very strict inclusion criterion was used (see discussion section of article 3.3), which resulted in a smaller number of patients in certain analyses (see article 3.3 MDD with co-morbid HIV/AIDS).
- The use of medical claims data did not provide any clinical information regarding the patients' progress or deterioration during the study period. Such an approach would have been useful if a correlation between AD usage during early vs. late stage HIV/AIDS and drug levels in MDD patients was required, which would provide further support of the non-compliance data.
- Patient interviews are also not possible when using medicine claims data, which could have been useful in order to determine an individual's direct reason for poor non-compliance.
- Compliance with prescribers' instructions could not be measured.
- Using medical claims data to establish the precise prevalence of TRD proved challenging, as TRD does not have a recognised ICD-10 code.

- For most of the central nervous system disorders, the ICD-10 codes were incomplete, and therefore no significant conclusions could have been made regarding TRD.
- In the current study, only pharmacological treatments could be considered. Psychological therapy was not considered.

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# **ADDENDUM 1: HUMAN PSYCHOPHARMACOLOGY: CLINICAL AND EXPERIMENTAL**

Author Guidelines

## **1. AIMS & SCOPE**

Human Psychopharmacology: Clinical and Experimental provides a forum for the evaluation of clinical and experimental research on both new and established psychotropic medicines. Experimental studies of other centrally active drugs, including herbal products, in clinical, social and psychological contexts, as well as clinical/scientific papers on drugs of abuse and drug dependency will also be considered. While the primary purpose of the Journal is to publish the results of clinical research, the results of animal studies relevant to human psychopharmacology are welcome. The following topics are of especial interest to the editors and readers of the Journal:

- All aspects of clinical psychopharmacology
- Efficacy and safety studies of novel and standard psychotropic drugs
- Studies of the adverse effects of psychotropic drugs
- Effects of psychotropic drugs on normal physiological processes
- Geriatric and paediatric psychopharmacology
- Ethical and psychosocial aspects of drug use and misuse
- Psychopharmacological aspects of sleep and chronobiology
- Neuroimaging and psychoactive drugs
- Phytopharmacology and psychoactive substances
- Drug treatment of neurological disorders
- Mechanisms of action of psychotropic drugs
- Ethnopsychopharmacology
- Pharmacogenetic aspects of mental illness and drug response
- Psychometrics: psychopharmacological methods and experimental design

Further information about the Journal, including links to the online sample copy and contents pages, can be found on the Journal homepage .

## **2. MANUSCRIPT CATEGORIES**

Human Psychopharmacology invites the following types of submission:

## **Research Articles**

Research Articles are the Journal's primary mode of scientific communication. Peer review of Research Articles will be handled by the most appropriate Editor .

## **Review Articles**

Authors who wish to submit an unsolicited review should first contact one of the Editors to determine its suitability for publication in the Journal. All Reviews will be peer-reviewed.

## **Short Communications**

Short research pieces and practical inferences from clinical observations will be considered, but should not exceed 1500 words. All Short Communications are peer-reviewed. Human Psychopharmacology will not accept Case Reports.

## **3. MANUSCRIPT SUBMISSION**

All submissions should be made online at the Human Psychopharmacology ScholarOne Manuscripts site (formerly known as Manuscript Central)— <http://mc.manuscriptcentral.com/hup> New users should first create an account. Once a user is logged onto the site, submissions should be made via the Author Centre.

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Manuscripts must be written in English.

Text should be supplied in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be supplied in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be supplied in jpg, tiff or eps format.

All manuscripts must be typed in 12pt font and in double space with margins of at least 2.5 cm.

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The first page of the manuscript should contain the following information:

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a running head not exceeding 50 characters

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### **Text**

This should in general, but not necessarily, be divided into sections with the headings: Introduction, Methods, Results, Discussion, Conclusion.

Generic or chemical names should be used for all compounds.

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Tables and figures should not be inserted in the appropriate place in the text but should be included at the end of the paper, each on a separate page.

Tables and figures should be referred to in text as follows: Figure 1, Figure 2; Table 1, Table 2. The place at which a table or figure is to be inserted in the printed text should be indicated clearly on a manuscript. Each table and/or figure must have a legend that explains its purpose without reference to the text.

The cost of printing colour illustrations in the Journal will be charged to the author at £600 per page. Colour figures may appear in the online edition free of charge.

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Taylor D, Paton C, Kerwin R. 2003. The Maudsley Prescribing Guidelines . Martin Dunitz: London.

Rabbitt PMA. 1982. How do old people know what to do next? In *Aging and Cognitive Processes* , Craik FIM, Trehub S (eds). Plenum Press: New York; 79-98.

Baune BT, Caliskan S, Todder T. 2007. Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. *Hum Psychopharmacol* 22 : 1-9.

(Titles of periodicals should be abbreviated according to the style used in Index Medicus.)

## **5. DECLARATION**

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Submission of a manuscript will be held to imply that it contains original unpublished work and is not being submitted for publication elsewhere at the same time. The author must supply a full statement to the Editor-in-Chief about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work.

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Acquisition of funding, the collection of data or general supervision of the research group, by themselves, do not justify authorship. All others who contributed to the work who are not authors should be named in the Acknowledgements section.

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OnlineOpen is available to authors of primary research articles who wish to make their article available to non-subscribers on publication, or whose funding agency requires grantees to archive the final version of their article. With OnlineOpen, the author, the author's funding agency, or the author's institution pays a fee to ensure that the article is made available to non-subscribers upon publication via Wiley Online Library, as well as deposited in the funding agency's preferred archive. For the full list of terms and conditions, see [http://wileyonlinelibrary.com/onlineopen#OnlineOpen\\_Terms](http://wileyonlinelibrary.com/onlineopen#OnlineOpen_Terms).

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### **Note to NIH Grantees**

Pursuant to NIH mandate, Wiley-Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, click [here](#)

## **ADDENDUM 2: SOUTH AFRICAN MEDICAL JOURNAL**

### Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

### **Authorship**

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to [www.icmje.org](http://www.icmje.org)).

### **Conflict Of Interest**

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

### **Research Ethics Committee Approval**

Provide evidence of Research Ethics Committee approval of the research where relevant.

### **PROTECTION OF PATIENT'S RIGHTS TO PRIVACY**

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to [www.icmje.org](http://www.icmje.org).

### **Ethnic Classification**

References to ethnic classification must indicate the rationale for this.

### **Manuscripts**

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. References should be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: Background, Objectives, Methods, Results, and Conclusion.

Scientific letters will be considered for publication as shorter Research articles.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAMJ peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: Background, Recommendations, Conclusion) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

### **Manuscript Preparation**

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - [www.icmje.org](http://www.icmje.org). Manuscripts must be provided in UK English.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) and '40 years of age'. The same applies to  $\pm$  and  $^{\circ}$ , i.e. '35 $\pm$ 6' and '19 $^{\circ}$ C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

## Illustrations And Tables

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as 'supplementary files'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: \* † ‡ § ¶ || then \*\* †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of high resolution/quality: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as 'supplementary files' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

## References

References must be kept to a maximum of 15. Authors must verify references from original sources. Only complete, correctly formatted reference lists will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by CrossRef.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

Book references: Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101.  
Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. *The World Health Report 2002 - Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '(Prof. Michael Jones, personal communication)'.

### **Proofs**

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, only typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

### **Changes Of Address**

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

### **Cpd Points**

Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article.

### **Charges**

There is no charge for the publication of manuscripts.

Please refer to the section on 'Guidelines' regarding the publication of supplements, where a charge may be applicable.

### **Submission Preparation Checklist**

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

Named authors consent to publication and meet the requirements of authorship as set out by the journal.

The submission has not been previously published, nor is it before another journal for consideration.

The text complies with the stylistic and bibliographic requirements in Author Guidelines.

The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.

Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).

For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.

Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).

An abstract has been included where applicable.

The research was approved by a Research Ethics Committee (if applicable)

Any conflict of interest (or competing interests) is indicated by the author(s).

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## ADDENDUM 3: AIDS RESEARCH AND THERAPY

### Instructions for authors

#### Research articles

[Submission process](#) | [Preparing main manuscript text](#) | [Preparing illustrations and figures](#) | [Preparing tables](#) | [Preparing additional files](#) | [Style and language](#)

See '[About this journal](#)' for descriptions of different article types and information about policies and the refereeing process.

#### Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that *AIDS Research and Therapy* levies an article-processing charge on all accepted Research articles; if the submitting author's institution is a [BioMed Central member](#) the cost of the article-processing charge may be covered by the membership (see [About](#) page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, *AIDS Research and Therapy* prefers [online submission](#).

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of [word processor](#) and [graphics file formats](#) that can be accepted for the main manuscript document by the online submission system. Additional files of any type, such as [movies](#), animations, or [original data files](#), can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the '[About AIDS Research and Therapy](#)' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editor-in-Chief and/or Editorial Board members.

Assistance with the process of manuscript preparation and submission is available from [BioMed Central customer support team](#).

We also provide a collection of links to useful tools and resources for scientific authors on our [Useful Tools](#) page.

## **File formats**

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use BioMed Central's TeX template)
- DeVice Independent format (DVI)

TeX/LaTeX users: Please use [BioMed Central's TeX template](#) and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

## **Preparing main manuscript text**

General guidelines of the journal's style and language are given [below](#).

## **Overview of manuscript sections for Research articles**

Manuscripts for Research articles submitted to *AIDS Research and Therapy* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Results and discussion
- Conclusions
- Methods
- List of abbreviations used (if any)
- Competing interests

- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions
- Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database ([EMBL](#)), DNA Data Bank of Japan ([DDBJ](#)), GenBank at the NCBI ([GenBank](#)), Protein Data Bank ([PDB](#)), Protein Information Resource ([PIR](#)) and the Swiss-Prot Protein Database ([Swiss-Prot](#)).

You can [download a template](#) (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the [About](#) section.

### **Title page**

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

### **Please note:**

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

### **Abstract**

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. Trial registration, if your research reports the results of a controlled health care intervention, please list your

trial registry, along with the unique identifying number (e.g. Trial registration: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

### **Keywords**

Three to ten keywords representing the main content of the article.

### **Background**

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

### **Results and discussion**

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

### **Conclusions**

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

### **Methods**

The methods section should include the design of the study, the type of materials involved, a clear description of all comparisons, and the type of analysis used, to enable replication.

### **List of abbreviations**

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

### **Competing interests**

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

### **Financial competing interests**

- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

### **Non-financial competing interests**

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

### **Authors' contributions**

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to [ICMJE guidelines](#), An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

### **Authors' information**

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

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The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

### **Endnotes**

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

### **References**

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and

unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding '*et al.*'..

Any *in press* articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

Style files are available for use with popular bibliographic management software:

- BibTeX
- EndNote style file
- Reference Manager
- Zotero

Examples of the *AIDS Research and Therapy* reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.

All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: **The Mouse Tumor Biology Database** [http://tumor.informatics.jax.org/mtbwi/index.do]. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

#### **Examples of the *AIDS Research and Therapy* reference style**

##### *Article within a journal*

Koonin EV, Altschul SF, Bork P: **BRCA1 protein products: functional motifs.** *Nat Genet* 1996,**13**:266-267.

##### *Article within a journal supplement*

Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I: **Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction.** *Proteins* 1999,**43**(Suppl 3):149-170.

##### *In press article*

Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

##### *Published abstract*

Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract].** *Arthritis Rheum* 1999, **42**:s250.

##### *Article within conference proceedings*

Jones X: **Zeolites and synthetic mechanisms.** In *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore*. Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

*Book chapter, or article within a book*

Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates.** In *Origins of Plastids. Volume 2.* 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

*Whole issue of journal*

Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology.** In *Breast Cancer Res* 1998, **10**:1-72.

*Whole conference proceedings*

Smith Y (Ed): *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.* Stoneham: Butterworth-Heinemann; 1996.

*Complete book*

Margulis L: *Origin of Eukaryotic Cells.* New Haven: Yale University Press; 1970.

*Monograph or book in a series*

Hunninghake GW, Gadek JE: **The alveolar macrophage.** In *Cultured Human Cells and Tissues.* Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): *Methods and Perspectives in Cell Biology*, vol 1.]

*Book with institutional author*

Advisory Committee on Genetic Modification: *Annual Report.* London; 1999.

*PhD thesis*

Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs.** *PhD thesis.* Stanford University, Computer Science Department; 1995.

*Link / URL*

**The Mouse Tumor Biology Database** [<http://tumor.informatics.jax.org/mtbwi/index.do>]

*Link / URL with author(s)*

Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values** [<http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/>]

*Dataset with persistent identifier*

Zheng, L-Y; Guo, X-S; He, B; Sun, L-J; Peng, Y; Dong, S-S; Liu, T-F; Jiang, S; Ramachandran, S; Liu, C-M; Jing, H-C (2011): **Genome data from sweet and grain sorghum (Sorghum bicolor).** *GigaScience.* <http://dx.doi.org/10.5524/100012>.

*Clinical trial registration record with persistent identifier*

Mendelow, AD (2006): **Surgical Trial in Lobar Intracerebral Haemorrhage.** *Current Controlled Trials.* <http://dx.doi.org/10.1186/ISRCTN22153967>

## **Preparing illustrations and figures**

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Please read our [figure preparation guidelines](#) for detailed instructions on maximising the quality of your [figures](#).

### **Formats**

The following file formats can be accepted:

PDF (preferred format for diagrams)

DOCX/DOC (single page only)

PPTX/PPT (single slide only)

EPS

PNG (preferred format for photos or images)

TIFF

JPEG

BMP

### **Figure legends**

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

### **Preparing tables**

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a landscape page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls ) or comma separated values (.csv). As with all files, please use the standard file extensions.

### **Preparing additional files**

Although *AIDS Research and Therapy* does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files **will be published** along with the article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files should be sent by email to [aidsrestherapy@gmail.com](mailto:aidsrestherapy@gmail.com), quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *AIDS Research and Therapy* requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data
- Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

### **Additional file formats**

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
  - PDF (Adobe Acrobat)
- Animations
  - SWF (Shockwave Flash)
- Movies
  - MP4 (MPEG 4)
  - MOV (Quicktime)
- Tabular data
  - XLS, XLSX (Excel Spreadsheet)
  - CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

### **Mini-websites**

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

- (1) Create a folder containing a starting file called index.html (or index.htm) in the root.
- (2) Put all files necessary for viewing the mini-website within the folder, or sub-folders.
- (3) Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
- (4) Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
- (5) Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

### **Style and language**

#### **General**

Currently, *AIDS Research and Therapy* can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

*AIDS Research and Therapy* will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

### **Help and advice on scientific writing**

The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on [Writing titles and abstracts for scientific articles](#).

Tim Albert has produced for BioMed Central a [list of tips](#) for writing a scientific manuscript. [American Scientist](#) also provides a list of resources for science writing. For more detailed guidance on preparing a manuscript and writing in English, please visit the [BioMed Central author academy](#).

### **Abbreviations**

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

### **Typography**

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.
- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.
- All pages should be numbered.
- Use the *AIDS Research and Therapy* [reference format](#).
- Footnotes are not allowed, but endnotes are permitted.
- Please do not format the text in multiple columns.
- Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

### **Units**

SI units should be used throughout (liter and molar are permitted, however).

## ADDENDUM 4: BMC PSYCHIATRY



IMPACT  
FACTOR 2.24

### Instructions for authors

#### Research articles

Criteria | Submission process | Preparing main manuscript text | Preparing illustrations and figures | Preparing tables | Preparing additional files | Style and language

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team. See 'About this journal' for information about policies and the refereeing process. We also provide a collection of links to useful tools and resources for scientific authors on our page.

#### Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our Editorial Policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

#### Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that BMC Psychiatry levies an article-processing charge on all accepted Research articles; if the submitting author's institution is a BioMed Central member the cost of the article-processing charge may be covered by the membership (see About page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, BMC Psychiatry prefers online submission.

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of word processor and graphics file formats that can be accepted for the main manuscript document by the online submission system. Additional files of any type, such as movies, animations, or original data files, can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the 'About BMC Psychiatry' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editorial team, Editorial Advisors, Section Editors and Associate Editors.

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team.

We also provide a collection of links to useful tools and resources for scientific authors on our Useful Tools page.

### **File formats**

The following word processor file formats are acceptable for the main manuscript document:

Microsoft word (DOC, DOCX)

Rich text format (RTF)

Portable document format (PDF)

TeX/LaTeX (use BioMed Central's TeX template)

DeVice Independent format (DVI)

TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

### **Publishing Datasets**

Through a special arrangement with LabArchives, LLC, authors submitting manuscripts to BMC Psychiatry can obtain a complimentary subscription to LabArchives with an allotment of 100MB of storage. LabArchives is an Electronic Laboratory Notebook which will enable scientists to share and publish data files in situ; you can then link your paper to these data. Data files linked to published articles are assigned digital object identifiers (DOIs) and will remain available in perpetuity. Use of

LabArchives or similar data publishing services does not replace preexisting data deposition requirements, such as for nucleic acid sequences, protein sequences and atomic coordinates.

Instructions on assigning DOIs to datasets, so they can be permanently linked to publications, can be found on the LabArchives website. Use of LabArchives' software has no influence on the editorial decision to accept or reject a manuscript.

Authors linking datasets to their publications should include an Availability of supporting data section in their manuscript and cite the dataset in their reference list.

### **Preparing main manuscript text**

General guidelines of the journal's style and language are given below.

### **Overview of manuscript sections for Research articles**

Manuscripts for Research articles submitted to BMC Psychiatry should be divided into the following sections (in this order):

Title page

Abstract

Keywords

Background

Methods

Results and discussion

Conclusions

List of abbreviations used (if any)

Competing interests

Authors' contributions

Authors' information

Acknowledgements

Endnotes

References

Illustrations and figures (if any)

Tables and captions

Preparing additional files

The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the About section.

### **Title page**

The title page should:

provide the title of the article

list the full names, institutional addresses and email addresses for all authors

indicate the corresponding author

### **Please note:**

the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"

abbreviations within the title should be avoided

### **Abstract**

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. Trial registration, if your research article reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. Trial registration: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

### **Keywords**

Three to ten keywords representing the main content of the article.

### **Background**

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a

search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

## **Methods**

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

For further details of the journal's data-release policy, see the policy section in 'About this journal'.

## **Results and discussion**

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

## **Conclusions**

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

## **List of abbreviations**

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

## **Competing interests**

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

### **Financial competing interests**

In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.

Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.

Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.

Do you have any other financial competing interests? If so, please specify.

### **Non-financial competing interests**

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

### **Authors' contributions**

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to ICMJE guidelines, An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

## **Authors' information**

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

## **Acknowledgements**

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

## **Endnotes**

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

## **References**

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding 'et al.'..

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

Style files are available for use with popular bibliographic management software:

BibTeX

EndNote style file

Reference Manager

Zotero

Examples of the BMC Psychiatry reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.

All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: The Mouse Tumor Biology Database [<http://tumor.informatics.jax.org/mtbwi/index.do>]. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

### **Examples of the BMC Psychiatry reference style**

#### **Article within a journal**

Koonin EV, Altschul SF, Bork P: BRCA1 protein products: functional motifs. *Nat Genet* 1996, 13:266-267.

#### **Article within a journal supplement**

Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I: Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction. *Proteins* 1999, 43(Suppl 3):149-170.

#### **In press article**

Kharitonov SA, Barnes PJ: Clinical aspects of exhaled nitric oxide. *Eur Respir J*, in press.

#### **Published abstract**

Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract]. *Arthritis Rheum* 1999, 42:s250.

#### **Article within conference proceedings**

Jones X: Zeolites and synthetic mechanisms. In *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore*. Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

#### **Book chapter, or article within a book**

Schnepf E: From prey via endosymbiont to plastids: comparative studies in dinoflagellates. In *Origins of Plastids. Volume 2. 2nd edition*. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

### **Whole issue of journal**

Ponder B, Johnston S, Chodosh L (Eds): Innovative oncology. In Breast Cancer Res 1998, 10:1-72.

### **Whole conference proceedings**

Smith Y (Ed): Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore. Stoneham: Butterworth-Heinemann; 1996.

### **Complete book**

Margulis L: Origin of Eukaryotic Cells. New Haven: Yale University Press; 1970.

### **Monograph or book in a series**

Hunninghake GW, Gadek JE: The alveolar macrophage. In Cultured Human Cells and Tissues. Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): Methods and Perspectives in Cell Biology, vol 1.]

### **Book with institutional author**

Advisory Committee on Genetic Modification: Annual Report. London; 1999.

### **PhD thesis**

Kohavi R: Wrappers for performance enhancement and oblivious decision graphs. PhD thesis. Stanford University, Computer Science Department; 1995.

### **Link / URL**

The Mouse Tumor Biology Database [<http://tumor.informatics.jax.org/mtbwi/index.do>]

### **Link / URL with author(s)**

Corpas M: The Crowdfunding Genome Project: a personal genomics community with open source values [<http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/>]

### **Dataset with persistent identifier**

Zheng, L-Y; Guo, X-S; He, B; Sun, L-J; Peng, Y; Dong, S-S; Liu, T-F; Jiang, S; Ramachandran, S; Liu, C-M; Jing, H-C (2011): Genome data from sweet and grain sorghum (*Sorghum bicolor*). GigaScience Database. <http://dx.doi.org/10.5524/100012>.

### **Clinical trial registration record with persistent identifier**

Mendelow, AD (2006): Surgical Trial in Lobar Intracerebral Haemorrhage. Current Controlled Trials. <http://dx.doi.org/10.1186/ISRCTN22153967>

### **Preparing illustrations and figures**

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of

separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Please read our figure preparation guidelines for detailed instructions on maximising the quality of your figures.

### **Formats**

The following file formats can be accepted:

PDF (preferred format for diagrams)

DOCX/DOC (single page only)

PPTX/PPT (single slide only)

EPS

PNG (preferred format for photos or images)

TIFF

JPEG

BMP

### **Figure legends**

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

### **Preparing tables**

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a portrait page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls ) or comma separated values (.csv). As with all files, please use the standard file extensions.

### **Preparing additional files**

Although BMC Psychiatry does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files will be published along with the article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files should be sent by email to [editorial@biomedcentral.com](mailto:editorial@biomedcentral.com), quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, BMC Psychiatry requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

#### **File name (e.g. Additional file 1)**

File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)

Title of data

#### **Description of data**

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

#### **Additional file formats**

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

## **Additional documentation PDF (Adobe Acrobat)**

Animations SWF (Shockwave Flash)

Movies MP4 (MPEG 4)

MOV (Quicktime)

Tabular data XLS, XLSX (Excel Spreadsheet)

CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

## **Mini-websites**

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.
2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

## **Style and language**

### **General**

Currently, BMC Psychiatry can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

BMC Psychiatry will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

### **Language editing**

For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz. BioMed Central has arranged a 10% discount to

the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. Please contact Edanz directly to make arrangements for editing, and for pricing and payment details.

### **Help and advice on scientific writing**

The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on Writing titles and abstracts for scientific articles.

Tim Albert has produced for BioMed Central a list of tips for writing a scientific manuscript. American Scientist also provides a list of resources for science writing. For more detailed guidance on preparing a manuscript and writing in English, please visit the BioMed Central author academy.

### **Abbreviations**

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

### **Typography**

Please use double line spacing.

Type the text unjustified, without hyphenating words at line breaks.

Use hard returns only to end headings and paragraphs, not to rearrange lines.

Capitalize only the first word, and proper nouns, in the title.

All lines and pages should be numbered. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.

Use the BMC Psychiatry reference format.

Footnotes are not allowed, but endnotes are permitted.

Please do not format the text in multiple columns.

Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.

### **Units**

SI units should be used throughout (liter and molar are permitted, however).

## ADDENDUM 5: APPROVAL OF ARTICLE 2

Page 1 of 1

>>> "Professor Janet Seggie" <janet.seggie@hmpg.co.za> 2014/08/13 11:38 AM >>>  
Dear Martha Susanne Luabe:

We have reached a decision regarding your submission to South African Medical Journal, 'Prospective analysis of the Medicine Possession Ratio (MPR) of antidepressants in the private health sector of South Africa (2006 to 2013)'.

Our decision is to accept on the strength of a favourable review (editing by that same reviewer - saving you the necessary revisions!)

Kind regards,

Professor Janet Seggie  
Phone 021 681 7200  
Fax 021 681 7035  
janet.seggie@hmpg.co.za

South African Medical Journal  
<http://www.samj.org.za>

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## ADDENDUM 6: APPROVAL OF ARTICLE 3

Page 1 of 1

>>> AIDS Research and Therapy Editorial <aidsrestherapy@gmail.com> 2014/12/01 05:37 PM >>>  
Article title: The impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: A prospective study in a South African private healthcare cohort  
MS ID : [1656535202134466](#)  
Authors : Francois N Slabbert, Brian H Harvey, Christian B Brink and Maelis S Lubbe  
Journal : AIDS Research and Therapy

Dear Prof Lubbe

Thank you for submitting a new version of your article.

A pdf file has been generated from your submitted manuscript and figures.

[http://www.aidsrestherapy.com/imedia/1656535202134466\\_article.pdf](http://www.aidsrestherapy.com/imedia/1656535202134466_article.pdf) (192K)

For your records, please find below link(s) to the correspondence you uploaded with this submission. Please note there may be a short delay in creating this file.

[http://www.aidsrestherapy.com/imedia/1847205986151959\\_comment1.pdf](http://www.aidsrestherapy.com/imedia/1847205986151959_comment1.pdf)

Best wishes,

The AIDS Research and Therapy Editorial team

e-mail: [aidsrestherapy@gmail.com](mailto:aidsrestherapy@gmail.com)  
Web: <http://www.aidsrestherapy.com/>

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