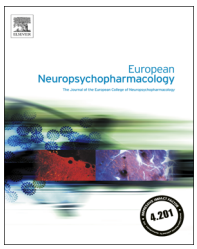
European Neuropsychopharmacology (2014) **24**, 1463–1474

www.elsevier.com/locate/euroneuro



A multivariate approach linking reported side effects of clinical antidepressant and antipsychotic trials to *in vitro* binding affinities

Johanna Michl[a], Christian Scharinger[b], Miriam Zauner[b], Siegfried Kasper[b], Michael Freissmuth[c], Harald H. Sitte[c], Gerhard F. Ecker[a,*], Lukas Pezawas[b]

[a]*Department of Pharmaceutical Chemistry, University of Vienna, Vienna, Austria*
[b]*Department of Psychiatry and Psychotherapy, Medical University Vienna, Vienna, Austria*
[c]*Department of Pharmacology, Medical University Vienna, Vienna, Austria*

Received 28 February 2014; received in revised form 23 June 2014; accepted 26 June 2014

KEYWORDS
Schizophrenia;
Depressive disorder;
Antidepressive agents;
Antipsychotic agents;
Clinical pharmacology;
Adverse effects

Abstract
The vast majority of approved antidepressants and antipsychotics exhibit a complex pharmacology. The mechanistic understanding of how these psychotropic medications are related to adverse drug reactions (ADRs) is crucial for the development of novel drug candidates and patient adherence. This study aims to associate *in vitro* assessed binding affinity profiles (39 compounds, 24 molecular drug targets) and ADRs ($n=22$) reported in clinical trials of antidepressants and antipsychotics ($n>59.000$ patients) by the use of robust multivariate statistics. Orthogonal projection to latent structures (O-PLS) regression models with reasonable predictability were found for several frequent ADRs such as nausea, diarrhea, hypotension, dizziness, headache, insomnia, sedation, sleepiness, increased sweating, and weight gain. Results of the present study support many well-known pharmacological principles such as the association of hypotension and dizziness with α_1-receptor or sedation with H_1-receptor antagonism. Moreover, the analyses revealed novel or hardly investigated mechanisms for

Abbreviations: 5-HT, 5-hydroxy tryptamine (serotonin); 5-HTT, serotonin transporter; AAP, atypical antipsychotics; ACH, acetylcholine; ADR, adverse drug reaction; AP, antipsychotic; CDSR, cochrane database of systematic reviews; CTZ, chemotrigger zone; DAT, dopamine transporter; EMA, european medicines agency; EPMS, extrapyramidal motor symptoms; FDA, food and drug administration; GI, gastrointestinal; K_i, inhibition constant; MAO, monoamine oxidase; MDD, major depressive disorder; NDRI, norepinephrine-dopamine re-uptake inhibitor; NET, norepinephrine transporter; O-PLS, orthogonal projection to latent structures; PDSP, psychoactive drugs screening program; p_1, principal component 1; pK_i, negative common logarithm of K_i; PRESS, prediction error sum of squares; SARI, serotonin antagonist and re-uptake inhibitor; SD, standard deviation; SNRI, serotonin norepinephrine re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor; TAP, typical antipsychotic; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant

*Corresponding author. Tel.: +43 1 4277 55110; fax: +43 1 4277 855110.
E-mail address: gerhard.f.ecker@univie.ac.at (G.F. Ecker).

http://dx.doi.org/10.1016/j.euroneuro.2014.06.013
0924-977X/

common ADRs including the potential involvement of 5-HT_6-antagonism in weight gain, muscarinic receptor antagonism in dizziness, or 5-HT_7-antagonism in sedation. To summarize, the presented study underlines the feasibility and value of a multivariate data mining approach in psychopharmacological development of antidepressants and antipsychotics.

1. Introduction

The development of more effective treatments of major neuropsychiatric disorders such as major depressive disorder (MDD) or schizophrenia is urgently needed due to their leading and unchanged role as contributors to global disease burden over the past two decades (Vos et al., 2012). Despite the doubtless beneficial effects of currently available antidepressants (ADs) and antipsychotics (APs), reported medication discontinuation rates are much higher than acceptable. Patient adherence is severely affected by adverse drug reactions (ADRs) (Insel, 2012), which are also an important factor leading to the attrition of clinical trials during drug development (Lounkine et al., 2012). Well-studied ADRs among many others include weight gain, sedation, extrapyramidal motor symptoms (EPMS), sexual dysfunction, and QT-interval prolongation (Castro et al., 2013). In contrast to other medical fields, pharmacological development in psychiatry is challenged by its unknown etiology and lack of biological meaningful diagnostic categories (Insel, 2012). Hence, ADs and APs have not been engineered based on prior knowledge of molecular pathways, but were identified by serendipity within the class of anti-histaminergic drugs (Lopez-Munoz and Alamo, 2009). Therefore, it is not surprising that numerous available ADs and APs target a broad spectrum of membrane proteins comprising receptors, transporters, and ion channels that result in complex pharmacological actions (Roth et al., 2004).

Over the past years, there has been an ongoing debate among scientists with regard to the benefits and harms of selective versus non-selective (Roth et al., 2004) as well as unimodal versus multimodal (Nutt, 2009) medications and their impact on observed efficacy and tolerability of psychopharmacological drug treatment. A major argument in favor of selectivity has been the broad clinical use of unimodal psychotropic medications such as selective serotonin re-uptake inhibitors (SSRIs) that demonstrated a more favorable side effect profile than older non-selective tricyclic antidepressants (TCAs) or early multimodal medications such as trazodone (Bauer et al., 2013; Grunze et al., 2013; Nutt, 2009). Considering the limitations of available meta-analyses (Huf et al., 2011) it has been suggested that increased selectivity has not lead to an overall improved antidepressive efficacy (Bauer et al., 2013), but instead led to a more acceptable side effect profile (Baghai et al., 2012). On the other hand, several non-selective medications including second-generation APs have been found to provide acceptable treatment efficacy without jeopardizing drug tolerability (Hasan et al., 2013). Given these counter-intuitive results with respect to drug selectivity, it becomes apparent that further research is urgently needed that facilitates the understanding on how receptor profiles of psychopharmacological medications translate into clinically observed ADRs. Ideally, inferences should be made from clinical trials investigating the occurrence of ADRs during the application of highly selective drugs that bind to single drug targets. However, most psychopharmacological compounds licensed for medical use are not selective and bind to a variety of drug targets. Therefore, inferences on the relationship between a specific receptor system and a specific ADR are difficult to extrapolate from a single compound. Hence, complimentary evidence stems from numerous drug safety studies in animals that inferred undesired drug effects from occupancy research to humans, a conclusion that has been criticized in the past.

Recently, alternative approaches have been developed including computational strategies that utilize information on the chemical structure of investigational drugs in order to predict ADRs (Bender et al., 2007; Lounkine et al., 2012). While such strategies are definitely novel and promote the understanding of drug structure-ADR relationships, methodological limitations exist including a restriction to single drug- (or off-) targets as well as the qualitative nature of these techniques. Since ADRs are likely to result from drug actions on multiple protein targets interacting with a variety of signaling pathways, a quantitative multivariate approach applied to large data sets may be more suitable and might be capable to detect associations that are otherwise impossible to deconvolute.

To demonstrate the feasibility and clinical plausibility of such a quantitative multivariate data analysis strategy, we performed an *orthogonal projections to latent structures (O-PLS)* analysis with the goal to associate binding affinity profiles of 39 antidepressants and antipsychotics licensed for medical use with high-quality ARDs data compiled from clinical trials comprising more than 59,000 patients. Both, binding and clinical data were extracted from publicly available databases. Our unprecedented approach verified some associations that had previously been suspected or less appreciated, *e.g.*, a prominent role of $5HT_6$-receptor blockage in triggering weight gain or a surprisingly large number of targets linked to sedation.

2. Experimental procedures

2.1. Data sources

Biological activities (K_i values) were retrieved from the openly accessible PDSP database (Psychoactive Drug Screening Program, http://pdsp.med.unc.edu). Reported side effect frequencies were extracted from the publically available Cochrane Database of Systematic Reviews (http://www.thecochranelibrary.com).