

# Nederlandse Ziekenhuisfarmaciedagen, 11 en 12 maart 2010

Dit artikel bevat de abstracts van de mondelinge presentaties tijdens de Nederlandse Ziekenhuisfarmaciedagen op 11 en 12 maart 2010 te Amersfoort. De digitale versie van dit artikel op [pw.nl](http://pw.nl) omvat ook de abstracts van de posterpresentaties.

## The contribution of renal impairment to preventable medication related hospital admissions

Anne Leendertse<sup>ab\*</sup>, Liesbeth van Dijk<sup>c</sup>, Peter de Smet<sup>d</sup>,  
Toine Egberts<sup>ab</sup> and Patricia van den Bemt<sup>be</sup>

<sup>a</sup> University Medical Centre Utrecht. <sup>b</sup> Utrecht Institute for Pharmaceutical Sciences, Utrecht University. <sup>c</sup> Vie Curi Medical Centre, Venlo. <sup>d</sup> Radboud University Nijmegen Medical Centre, Nijmegen. <sup>e</sup> Erasmus Medical Center, Rotterdam.

\* Correspondence: [aleende2@umcutrecht.nl](mailto:aleende2@umcutrecht.nl).

### Background

Medication errors related to impaired renal function, such as lack of monitoring of renal function, ignoring or non-compliance with dosing guidelines, frequently occur in the inpatient setting, which can lead to severe adverse drug events. Whether clinically relevant errors occur as often within the outpatient setting is less well known. Therefore we analyzed the medication related hospital admissions from the HARM (Hospital Admissions Related to Medicationstudy [1]) to determine the extent to which renal impairment contributes to preventable hospital admissions due to medication errors.

### Methods

For all included cases in the HARM-study creatinine levels were collected and creatinine clearance was estimated by using the Jelliffe-II formula [2]. These patients were divided into three groups based on the availability of creatinine levels: group A, the home-monitored group, group B, the in-hospital-monitored group and group C, the non-monitored group. All HARM-cases were assessed on a causal relationship between renal function and the admission and if a medication error such as a drug–drug interaction, inappropriate dosing or a drug–disease interaction as described in the national guideline renal impairment [3, 4] was present.

### Results

Serum creatinine before admission to hospital was available in 30.8% (227) of the 714 patients included in the HARM-study (group A). From 58.8% (420) of the patients, creatinine levels were available only on admission to hospital (group B). From 9.4% (67) of the patients renal function was not available (group C). The groups A, B and C did not differ with respect to general characteristics such as age, gender, morbidity or medication, but patients in group C had significantly less registered diseases. After assessment 70 admissions (10%) were related to medication and to renal impairment (29 from group A, 41 from group B and none from group C). A dosing error was found in 46 patients (14 in group A and 32 in group B), a drug–drug interaction in 22 patients (13 in group A and 9 in group B) and a drug–disease interaction in 17 patients (10 in group A and 7 in group B).

### Conclusions

Renal impairment and medication may lead to medication related hospital admissions. From these admissions in the hospital-monitored group B we conclude that monitoring renal function is relevant and can probably prevent admissions. Although the renal function in group A was monitored, relevant medication errors occur in this group, therefore we conclude that adjusting pharmacotherapy according to the renal function is relevant and may prevent hospital admissions.

### REFERENCES

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Keywords: medication safety – medication error – renal impairment – hospital admission – adverse drug event

## The use of serotonergic antidepressants and changes in blood pressure

I.M.M. van Haelst<sup>ax</sup>, W.A. van Klei<sup>b</sup>, H.J. Doodeman<sup>a</sup>,  
C.J. Kalkman<sup>b</sup> and A.C.G. Egberts<sup>c</sup>

<sup>a</sup> Hospital Pharmacy, Medical Center Alkmaar, Alkmaar. <sup>b</sup> Department of Perioperative Care & Emergency Medicine, University Medical Center Utrecht.

<sup>c</sup> Department of Clinical Pharmacy, University Medical Center Utrecht, and Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University.

\* Correspondence: [i.van.haelst@mca.nl](mailto:i.van.haelst@mca.nl).

### Background

Selective serotonin reuptake inhibitors (SSRIs) have been associated with an increase in blood pressure but evidence is scarce. As blood pressure is closely monitored during anaesthesia, we considered that routine intraoperative hemodynamic data can be used to get an estimate of a potential effect. Normally, side effects of anaesthetics result in a decrease in blood pressure. This study aimed to estimate the association between the use of SSRIs and changes in blood pressure by measuring the occurrence of intra-operative hyper- and hypotension.

## Methods

We conducted a retrospective cohort study among patients who underwent elective primary total hip arthroplasty in the period from 1 July 2004 until 1 July 2008. The index group included all users of both serotonergic and non-serotonergic antidepressants. The reference group included a random sample (ratio 1:3) of non-users. The outcome was an episode of decreased or increased blood pressure defined as a change in blood pressure of 30% or more compared to baseline. Number, mean duration, total duration and area under the curve (AUC) of these episodes were recorded.

## Results

The index group included 22 users of SSRIs and 15 users of non-serotonergic antidepressants. The reference group included 111 patients. After adjustment for confounding factors, users of SSRIs showed less hypotensive episodes, a shorter mean and total duration of these episodes and a smaller AUC when compared to the reference group. These effects were statistically significant for the number of episodes (mean difference 1.1, 95% CI: 0.01-2.19) and total duration (mean difference 28.8 minutes, 95% CI: 10.0-47.5). This effect was not observed in users of non-serotonergic antidepressants. The occurrence of hypertensive episodes did not differ between groups.

## Conclusions

The use of SSRIs is associated with an increase in blood pressure shown as a significantly decreased number and total duration of intraoperative hypotensive episodes.

Keywords: serotonergic antidepressants – blood pressure – intraoperative

## Association between the alpha-2a-adrenergic receptor 1291 C/G polymorphism and the metabolic syndrome in patients using antipsychotics

Arne J. Risselada<sup>ab\*</sup>, Jelle Vehof<sup>fd</sup>, Richard Bruggeman<sup>f</sup>, Bob Wilffert<sup>e</sup>, Dan Cohen<sup>d</sup>, Asmar F. Al Hadithy<sup>eh</sup>, Johan Arends<sup>cd</sup> and Hans Mulder<sup>ab</sup>

<sup>a</sup> Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences. <sup>b</sup> Department of Clinical Pharmacy, Wilhelmina Hospital, Assen. <sup>c</sup> Mental Health Services Drenthe, Assen. <sup>d</sup> Mental Health Services GGZ-NHN, Heerhugowaard. <sup>e</sup> Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen. <sup>f</sup> Department of Psychiatry, University Medical Centre Groningen. <sup>g</sup> Department of Epidemiology, University Medical Centre Groningen. <sup>h</sup> Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam.

\* Correspondence: arne.risselada@wza.nl.

## Background

The adrenergic alpha-2a receptor plays an important role in lipolysis. Two studies in Asians have found an association between the 1291 C/G polymorphism, located in the gene coding for the alpha-2a receptor (ADRA2A), and antipsychotic-induced weight gain. Carriership of the 1291 G-allele resulted in more antipsychotic-induced weight gain. A study in Caucasians found a protective effect of the 1291-G-allele in antipsychotic-induced weight gain. The objective of the current study was to investigate the association between the ADRA2A 1291 C/G polymorphism and the metabolic syndrome.

## Methods

This study included patients from three different patient populations. A cross-sectional design was used to assess the association between ADRA2A 1291 C/G genotype and the metabolic syndrome in patients diagnosed with schizophrenia or related disorders. Patients,  $\geq 18$  years, were eligible for inclusion if they used antipsychotic drugs. Primary endpoint was prevalence of the metabolic syndrome, as defined by the ATP IIIa criteria. HbA1c was used when fasting glucose values were unavailable. Secondary endpoints were associations between the 1291 C/G polymorphism and individual parameters contributing to the metabolic syndrome, as well as effects of individual antipsychotics. Primary determinant was the genotype of the 1291 C/G polymorphism located in the ADRA2A gene. The association between carriership of the variant 1291 G-allele and prevalence of the metabolic syndrome was investigated with logistic regression. Results were expressed as odds ratios with a 95% confidence interval (95% CI). Data were investigated for confounding effects of age, HTR2c-genotype, ethnicity, DSM-IV diagnosis, gender and antipsychotic drugs.

## Results

In total, 470 patients, mainly male (68%) and Caucasian (94%), were included. There was no significant association between carriership of the variant 1291 G-allele and prevalence of the metabolic syndrome (OR 0.73; 95% CI 0.49-1.15). There was a trend for a protective effect of carriership of the variant G-allele for reaching the triglyceride cut-off point of 1.7 mmol/l (adjusted OR 0.67; 95%CI: 0.44-1.001,  $p$  0.051). Exploratory analysis showed an association between carriership of the variant 1291 G-allele and a reduced prevalence of the metabolic syndrome in patients not currently using antipsychotics (OR 0.05; 95% CI 0.003-0.97,  $p$  0.048).

## Conclusions

This study shows that the ADRA2A 1291 C/G polymorphism does not appear to be a strong predictor for long term occurrence of the metabolic syndrome in patients using antipsychotic drugs.

Keywords: ADRA2A – antipsychotics – metabolic syndrome – schizophrenia – 1291 C/G

## Paediatric overdose alerting in computerized physician order entry still immature

Heleen van der Sijs <sup>\*</sup>, Serpil Huy and Lidwien M. Hanff

Erasmus University Medical Center, Rotterdam.

\* Correspondence: i.vandersijs@erasmusmc.nl.

### Background

Computerized physician order entry (CPOE) systems frequently include drug safety alerting. A safe alerting system generates alerts in all dangerous situations and presents patient specific alerts that do not unnecessarily disrupt workflow. Functionality on paediatric overdose alerting per kg bodyweight is new in the CPOE Medicatie/EVS. Before implementation, we investigated whether this new functionality would result in a safe alerting system. Sensitivity and (unnecessary) workflow disruptions were measured with the current and new overdose alerting functionality.

### Methods

All inpatients on paediatric medium care wards of Erasmus MC-Sophia on one index date were analyzed for age, number of orders and subspecialty. A broad selection of 33 patients of different subspecialties and age were included in the study. The number of overdose alerts in the current CPOE were counted. All medication orders of these patients were entered in the new version of the CPOE with overdose alerts per kg bodyweight. Indication inquiries and overdose alerts were counted, as well as nonintrusive warnings that dose checking could not take place. The relevance of indication inquiries and overdose alerts were analyzed.

### Results

On 8 June 2008, 80 patients were present on paediatric medium care wards of Erasmus MC-Sophia. They had been prescribed 950 medication orders. 33 patients with 560 orders were included for further analysis. The percentage overdose alerts per prescribed order was 3.8% with the current and 10.5% with the new functionality. However, in the new functionality 35.2% of the orders showed nonintrusive warning icons that dose checking was impossible, because of lack of data in the national database (16.6%), mainly for young children, manufactured drugs or local database adjustments (14.5%) or use of free text (4.1%). The new functionality caused workflow disruptions (for alerts or indication inquiries) in 38% of cases, and only 33% of these disruptions were relevant. The system asked to select an indication in 27.5% of prescribed orders, but this was relevant only in 21% of cases. 36% of the overdose alerts were perceived irrelevant because these fell within the 120% range.

### Conclusion

The new functionality for paediatric overdose alerting showed too

low sensitivity, mainly because of lack of data for young children in the national drug database. Furthermore, it resulted in too many unnecessary workflow disruptions because of irrelevant indication inquiries and alerting for small overdoses. The new functionality was not safe enough for implementation. Adjustments in CPOE and national drug database are required.

Keywords: computerized physician order entry – patient safety – paediatrics – computer-assisted drug therapy – error management

## Effect of genetic polymorphisms in genes encoding GST isoenzymes on busulfan clearance in adult patients undergoing hematopoietic stem cell transplantation

M.H. ten Brink <sup>a\*</sup>, J. Zwaveling <sup>a</sup>, R.J.H.M. van der Straaten <sup>a</sup>, P.A. von dem Borne <sup>b</sup>, J. den Hartigh <sup>a</sup>, H-J. Guchelaar <sup>a</sup> and J.A.M. Wessels <sup>a</sup>

<sup>a</sup> Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center. <sup>b</sup> Department of Hematology, Leiden University Medical Center.

\* Correspondence: m.h.ten\_brink@lumc.nl.

### Background

Highdose busulfan is frequently used in conditioning regimens prior to hematopoietic stem cell transplantations (HSCT). However, high busulfan exposure is associated with toxicity like veno-occlusive disease and mucositis, whereas low busulfan exposure leads to higher rates of graft failure and rejection. Although busulfan dosing is based on body weight or body surface area, a high interindividual variability in exposure is still observed. As a result, treatment with busulfan in clinical practice is often individualized by therapeutic drug monitoring. Variability in busulfan exposure could be assigned to variability in busulfan metabolism, with glutathione conjugation by glutathione S-transferases (GSTs) as primary route of elimination. Therefore, we hypothesize that polymorphisms in genes encoding for the GSTs GSTA1, GSTM1 and GSTP1 are associated with busulfan exposure in patients undergoing HSCT.

### Methods

69 adult patients received busulfan as part of their HSCT conditioning regimen. Dosing was adjusted to body weight (0.8 mg/kg) and was given 4 times daily during 2 or 4 days in a nonmyeloablative or myeloablative regimen, respectively. Busulfan was administered intravenously during 2 hours. Plasma drug level measurements were performed at 2.5 and 4.0 hours after start of the first infusion on day one of treatment. The following genetic variants were determined: -69C/T in GSTA1, 313A/G in GSTP1 and null allele of GSTM1.

Population pharmacokinetic parameters (clearance and volume of distribution) were estimated using a one-compartment model with iterative two-stage Bayesian fitting. Individual pharmacokinetic parameters (clearance and elimination half-life) were calculated by using the method of least squares, in MW/Pharm. Associations with individual busulfan clearance and polymorphisms were tested with ANOVA or Student's t-test in SPSS. P-values <0.05 were considered significant.

### Results

Patients with *GSTA1* \*A/\*A genotype had a higher busulfan clearance ( $0.216 \pm 0.054 \text{ l}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ ) compared to patients with *GSTA1* \*A/\*B ( $0.177 \pm 0.041 \text{ l}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ ) and *GSTA1* \*B/\*B ( $0.155 \pm 0.039 \text{ l}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ );

presented as mean  $\pm$  SD,  $p = 0.001$ . These differences could not be associated with clinical outcomes. There was no relation between polymorphisms in *GSTM1* and *GSTP1* and busulfan clearance.

### Conclusions

This study shows that carriership of the \*B-allele in *GSTA1* results in a decrease of busulfan clearance, whereas no associations were found between *GSTM1* and *GSTP1* genotypes and busulfan clearance.

Keywords: busulfan – haemopoietic stem cell transplantations – GST polymorphism – population pharmacokinetics

## De digitale versie van dit artikel op pw.nl bevat ook de abstracts van de volgende posterpresentaties

Limited sampling strategies for therapeutic drug monitoring of linezolid in MDR-TB patients

Antipsychotic-induced weight gain and rs1455832 polymorphism of the *ROBO1* gene: association analysis in psychosis patients on anti-psychotics

VEGF-SPECT with  $^{111}\text{In}$ -bevacizumab in stage III/IV melanoma patients

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The impact of two manual medication cart filling methods on the frequency of medication administration errors: a prospective before and after study

Clinical rule for drug dose adjustments in neonates and infants with renal impairment

Effect of cytochrome P450 2C9 polymorphisms on dose and time to stable dose of sulfonylurea in primary care type 2 diabetes mellitus patients

Unexpected high vancomycin levels; aberrant pharmacokinetics due to increased protein binding of vancomycin

An exploratory pharmacogenetic pathway approach to detect associations with adalimumab efficacy in rheumatoid arthritis

## Limited sampling strategies for therapeutic drug monitoring of linezolid in MDR-TB patients

Jan-Willem C. Alffenaar <sup>a,x</sup>, Jos G.W. Kosterink <sup>a</sup>, Richard van Altena <sup>b</sup>, Tjip S. van der Werf <sup>c</sup>, Donald R.A. Uges <sup>a</sup> and Johannes H. Proost <sup>d</sup>

<sup>a</sup> Department of Hospital and Clinical Pharmacy, University Medical Center Groningen, University of Groningen. <sup>b</sup> Tuberculosis Center Beatrixoord, University Medical Center Groningen, University of Groningen, Haren. <sup>c</sup> Departments of Internal Medicine, and Pulmonary Diseases & Tuberculosis, University Medical Center Groningen, University of Groningen. <sup>d</sup> Department of Pharmacokinetics, Toxicology and Targeting, University Center for Pharmacy, University of Groningen.

\* Correspondence: j.w.c.alffenaar@apoth.umcg.nl.

### Background

Linezolid is a potential drug for the treatment of multidrug resistant tuberculosis but its use is limited because of severe adverse effects like anaemia, thrombocytopenia and peripheral neuropathy. This study aimed to develop a model for the prediction of linezolid area under the plasma concentration-time curve from 0 to 12 hours ( $AUC_{0-12h}$ ) by limited sampling strategy to enable individualised dosing.

### Methods

14 MDR-TB patients received linezolid twice daily as part of their anti-tuberculosis treatment. Linezolid concentrations were determined at steady state by high-performance liquid chromatography tandem mass spectrometry before and at 1, 2, 4, 8 and 12 hours after dosing. Linezolid  $AUC_{0-12h}$ , population model and limited sampling models were calculated with MW/Pharm software. A linezolid population one-compartment model with first-order absorption pharmacokinetics without lag time was generated from the linezolid dosing of 600 mg twice daily, the body surface area of the patients, and the observed linezolid serum concentrations, using an iterative two-stage Bayesian procedure. Limited sampling models (LSM) were calculated using Monte Carlo data simulation. The correlation between predicted linezolid  $AUC_{0-12h}$  and observed linezolid  $AUC_{0-12h}$  was investigated by Bland-Altman analysis.

### Results

A total of 26 pharmacokinetic profiles were obtained. The median  $AUC_{0-12h}$  was 51.8 (IQR 41.8-65.9) mg\*h/l at 300 mg, and 123.8 (IQR 100.9-152.5) mg\*h/l at 600 mg both twice daily. The clinically most relevant model for prediction of linezolid  $AUC_{0-12h}$  employed a linezolid trough level [ $r = 0.91$ , prediction bias = -2.9% and root mean square error (RMSE) = 15%]. The population model showed that the  $AUC/MIC$  ratio, using the estimated  $AUC$  based on a trough level, did not differ significantly from the calculated ratio based on multiple samples. The difference between choosing a trough concentration and two to three samples increased the correlation from 0.90 to 0.95, but appeared not clinically relevant as it did not result in a different dosage advice.

### Conclusion

This study showed that linezolid  $AUC_{0-12h}$  in MDR-TB patients could be predicted accurately by minimal sampling strategy and can be used to individualize the dose.

Keywords: MDR-TB – linezolid – TDM – pharmacokinetics – limited sampling

## Antipsychotic-induced weight gain and rs1455832 polymorphism of the ROBO1 gene: association analysis in psychosis patients on antipsychotics

Jelle Vehof <sup>a</sup>, Asmar F.Y. Al Hadithy <sup>b,x</sup>, Huibert Burger <sup>a</sup>, Arne J. Risselada <sup>c</sup>, Bob Wilffert <sup>d</sup>, Dan Cohen <sup>f</sup>, Johan Arends <sup>g</sup>, Hans Mulder <sup>ee</sup> and Richard Bruggeman <sup>a</sup>

<sup>a</sup> University Medical Centre Groningen. <sup>b</sup> Erasmus University Medical Centre, Rotterdam. <sup>c</sup> Wilhelmina Hospital, Assen. <sup>d</sup> University of Groningen. <sup>e</sup> Utrecht Institute for Pharmaceutical Sciences, Utrecht University. <sup>f</sup> Mental Health Services GGZ-NHN, Heerhugowaard. <sup>g</sup> Mental Health Services Drenthe, Assen.

\* Correspondence: a.alhadithy@erasmusmc.nl.

### Background

Weight gain is one of the major problems in patients using antipsychotic medication. Antipsychotic-induced weight gain and obesity have been associated with relevant morbidities and reduced compliance to pharmacotherapy. It has been suggested that certain genetic risk factors may predispose to antipsychotic-induced weight gain. Knowledge of these factors may facilitate individualized pharmacotherapy in the future antipsychotics. Recently, an association has been reported between a SNP (rs1455832) of the roundabout axon guidance receptor, homolog 1 (ROBO1) gene and obesity in persons younger than 30 years. The association has been replicated by five of eight additional cohorts comprising in total 13,584 individuals [Am J Hum Genet. 2008;82:849-58]. The aim of the current study is to investigate the association between BMI and rs1455832 in patients with a psychotic disorder using antipsychotics.

### Methods

A cross-sectional design was used to assess the association between rs1455832 polymorphism and body mass index (BMI) in a pooled sample of Caucasian psychiatric patients obtained from three comparable Dutch psychiatric populations. Patients were eligible for inclusion in this study if they met DSM-IV criteria for a non-affective psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder NOS), were 18 years or older, and used one or more antipsychotics. Genotyping was conducted according to standard protocols. Linear (for BMI) and logistic (for obesity, defined as BMI >30) regression analyses, corrected for age and gender, were applied in the statistical analyses.

### Results

A total of 435 patients were included in the present association

analyses. The rs1455832 polymorphism studied was significantly associated with BMI and obesity in female patients. Female patients had a statistically significant ( $p = 0.020$ ) decrease of 1.78 kg/m<sup>2</sup> in BMI values per C-allele. In contrast to females, this association was not exhibited in male patients.

### Conclusion

The rs1455832 polymorphism may play a role in inducing obesity in female patients using antipsychotics.

Keywords: ROBO1 – antipsychotics – obesity – pharmacogenetics

## VEGF-SPECT with <sup>111</sup>In-bevacizumab in stage III/IV melanoma patients

Marjolijn N. Lub-de Hooge <sup>\*</sup>, Wouter B. Nagengast, Esther M.E. van Straten, Adrienne H. Brouwers, Wilfred F.A. den Dunnen, Johan R. de Jong, Harry Hollema, Jos G.W. Kosterink, Rudi A. Dierckx, Nanno H. Mulder, Elisabeth G.E. de Vries, Harald J. Hoekstra and Geke A.P. Hospers  
University Medical Center Groningen.

\* Correspondence: m.n.de.hooge@apoth.umcg.nl.

### Background

Vascular endothelial growth factor (VEGF) plays an important role in tumour angiogenesis, the forming of new blood vessels. Bevacizumab is a monoclonal antibody that targets VEGF. <sup>111</sup>In-bevacizumab was developed for VEGF visualization. Several factors point to a role for VEGF in melanoma. Aim of this feasibility study is to investigate the presence of VEGF in melanoma lesions by VEGF-SPECT with <sup>111</sup>In-bevacizumab and to compare VEGF-SPECT tumor visualization with CT and FDG-PET imaging.

### Methods

Eligible were patients with stage III/IV melanoma who required surgical resection of involved lymph nodes. VEGF-SPECT was performed after administration of 100 MBq <sup>111</sup>In-bevacizumab (8 mg) day 0 on days 0, 2, 4 and 7 post injection. Tumour visualization and quantification was compared with CT and FDG-PET imaging.

### Results

9 patients were included. FDG-PET and CT detected each in total 12 lesions. All lesions were also visualized by VEGF-SPECT. VEGF-SPECT tumour visualization was optimal at day 4 post injection of <sup>111</sup>In-bevacizumab due to slow antibody pharmacokinetics. A 3-fold difference in <sup>111</sup>In-bevacizumab tumour uptake was detected among tumour lesions. In addition, <sup>111</sup>In-bevacizumab uptake varied between tumour lesions within patients and within lesions, suggesting differences in VEGF-levels.

### Conclusions

VEGF-SPECT could visualize melanoma lymph node metastasis,

comparable to CT and FDG-PET. Large variation in <sup>111</sup>In-bevacizumab uptake was detected. Future studies should elucidate the potential role of VEGF-SPECT in the selection of patients for individualized anti-angiogenic therapy.

Keywords: VEGF – melanoma – immunoSPECT – bevacizumab

## Interventions by hospital pharmacists to prevent gastrointestinal complications

M. Duyvendak <sup>ab\*</sup>, H.W. Bakker <sup>ac</sup> and J. Arts <sup>a</sup>

<sup>a</sup> Clinical Pharmacy, Antonius Hospital, Sneek. <sup>b</sup> Pharmacotherapy & Pharmaceutical Care, University of Groningen. <sup>c</sup> Clinical Pharmacy, Medical Centre Alkmaar.

\* Correspondence: m.duyvendak@antonius-sneek.nl.

### Background

The HARM-study showed gastrointestinal complications of NSAIDs or platelet inhibitors being the number one cause of drug related hospital admissions. Aim of this study was to determine the effect of a hospital pharmacy-based intervention to identify patients at risk and advocate the start of preventive treatment. Secondly, we assessed the benefits of a clinical rule based decision support system over a drug–drug interaction model.

### Methods

Patients at risk were identified using the criteria from the HARM-wrestling report, consecutively using the drug–drug interaction based model and a clinical rule decision support system. The sensitivity and specificity of both models were determined by comparison with a manual determination of the need for gastroprotection using a list of all patients receiving NSAID and/or platelet inhibitors. The hospital pharmacist discussed intervention proposals with the physician of the patient.

### Results

In 12% (103/851) of patients an intervention was carried out. This was 50% (103/206) of patients at risk that did not yet receive proton pump inhibitors. The proportion of interventions was significantly higher using a clinical rule versus a drug–drug interaction based model. Furthermore the sensitivity (91 vs 36%) and specificity (97 vs 21%) of the clinical rule were significantly higher, resulting in fewer alerts.

### Conclusion

The results show that a hospital pharmacy based intervention is successful for identifying and treating patients at risk of gastrointestinal complications of NSAIDs and platelet inhibitors. Moreover, a clinical rule based decision support system significantly improves patient safety due to the higher sensitivity and specificity compared to a drug–drug interaction based model.

Keywords: clinical rules – medication safety – gastroprotection – HARM-Wrestling – acetylsalicylic acid – intervention

## Transitions from general practitioner to psychiatrist care (or vice versa) during a first antidepressant treatment episode

Helga Gardarsdottir<sup>ab\*</sup>, Toine C. G. Egberts<sup>ab</sup> and Eibert R. Heerdink<sup>ab</sup>

<sup>a</sup> Department of Clinical Pharmacy, University Medical Centre Utrecht.

<sup>b</sup> Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University.

\* Correspondence: h.gardarsdottir@umcutrecht.nl.

### Background

While recent pharmacoepidemiologic studies on antidepressant drug use focus mainly on patients initiating use in general practice (GP) or specialist care, little is known about the frequency of transition from GP to specialist care or vice versa once antidepressant treatment has started. The objective of this study was to investigate how frequently patients transit in care, from GP to psychiatrist and vice versa, during a first antidepressant episode and antidepressant treatment changes associated with those transitions.

### Methods

Antidepressant treatment episodes were constructed for patients ( $\geq 18$  years) initiating SSRI use in 2000 in the Netherlands ( $n = 10,158$ ). The frequency of transition in care within a first treatment episode was investigated. Changes in antidepressant treatment were compared between transiting and non-transiting patients by conducting two matched cohort studies nested within the antidepressant users' cohort. Changes in antidepressant treatment, such as switching, dose adjustment (higher DDDs and lower DDDs prescribed) were compared for transiting and non-transiting users using the Cox proportional hazards model.

### Results

6% of patients who initiate SSRI use in GP transited to psychiatrist care, whereas 39.1% of those initiating use in psychiatrist care transited to GP care. Males and younger patients had a significantly higher risk of transiting from GP to psychiatrist care. Patients transiting from GP to psychiatrist care were more likely to switch to other antidepressants (RR = 6.16, 95% CI 4.90-7.75) or to other doses (RR = 4.48, 95% CI 3.76-5.34) than non-transiting patients. No significant differences in patient characteristics or antidepressant treatment were found for patients transiting from psychiatric to GP care.

### Conclusion

Approximately 9% of SSRI initiators transit in care. Studies have shown that those who initiate SSRI use in psychiatrist care are more likely to be male and younger. Our study shows that this also applies to patients who transit from GP to psychiatrist care. Transitions from GP to psychiatric care lead to antidepressant treatment changes and could potentially be used in observational studies as a disease severity indicator.

Keywords: antidepressive agents – episode of care – pharmacoepidemiology – physician – transition

## Medication reconciliation at admission and discharge

F. Karapinar<sup>ab\*</sup>, S.D. Borgsteede<sup>c</sup>, M.J.A. Janssen<sup>a</sup>, A.C.G. Egberts<sup>bd</sup> and P.M.L.A. van den Bemt<sup>be</sup>

<sup>a</sup> Department of clinical pharmacy, Sint Lucas Andreas Hospital,

Amsterdam. <sup>b</sup> Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University. <sup>c</sup> Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch. <sup>d</sup> Department of clinical pharmacy, University Medical Centre Utrecht. <sup>e</sup> Department of clinical pharmacy, Erasmus Medical Centre, Rotterdam.

\* Correspondence: f.karapinar@slaz.nl.

### Background

To prevent medication errors at transition points, such as hospital admission and discharge, medication reconciliation has been developed [1]. With medication reconciliation discrepancies between medication prescribed in hospital and medication used before admission are eliminated, the pharmacotherapy is optimised, changes are documented and the discharge information is communicated to the next healthcare provider [2]. Previous studies mainly focused on the elimination of discrepancies at hospital admission [3, 4]. Furthermore, the patient is not always involved in medication reconciliation [5-9]. The aim of this study is to evaluate the amount and type of interventions with medication reconciliation at different transition points.

### Methods

An observational study was performed at the Sint Lucas Andreas Hospital. Patients from the cardiology department were included from June to July 2008. Exclusion criteria were: no chronic medication use, discharge to a nursing home or out of office hours and patients unable to be counselled (physical, mental or language restrictions). At hospital admission and discharge a pharmacy team optimised the medication prescribed in hospital and eliminated discrepancies with the medication used before admission by using community pharmacy medication records. Hereafter patient counselling was performed at discharge to inform the patient about the medication changes and finally the discharge information was sent to the next healthcare provider (e.g. community pharmacist and general practitioner). Outcome parameters were the amount and type of interventions registered. Data were analysed with descriptive statistical analysis.

### Results

In the study 171 patient were included. We registered at least one intervention in all patients. At hospital admission discrepancies were eliminated in 69.0% of patients. However, at discharge discrepancies were still corrected in 59.1% of patients (e.g. restarting temporarily

discontinued medication). Furthermore, at discharge the medication was optimised in 72.5% of patients (e.g. discontinue hypnotics). With patient counselling the medication use was optimised in 86.5% of patients (e.g. prevention of side effects). Patients also gave information on how they used the medication and which medication was (not) needed.

## Conclusion

This research shows that in all patients at least one intervention could be registered. Medication reconciliation is therefore important at different transition points to eliminate discrepancies, to optimise pharmacotherapy and to inform the patient and the next healthcare provider about the medication changes and reasons for it.

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Keywords: hospital admission – hospital discharge – medication reconciliation – patient counselling

## Incidence of contrast-induced nephropathy (CIN) in out-hospital patients undergoing iodinated contrast-enhanced CT scans after implementation of a CIN prevention protocol

H.J. Kingma <sup>a\*</sup>, R.W.F. Geenen <sup>b</sup>, P.R. Algra <sup>b</sup>, F. Tegelaers <sup>c</sup>, W.A. Bax <sup>d</sup>, H.J. Doodeman <sup>a</sup>, T. van der Ploeg <sup>e</sup> and I.M.M. van Haelst <sup>a</sup>

<sup>a</sup> Hospital Pharmacy; <sup>b</sup> Department of Radiology; <sup>c</sup> Laboratory for Clinical Chemistry, Immunology and Haematology; <sup>d</sup> Department of Nephrology; <sup>e</sup> statistician, Foreest Institute; Medisch Centrum Alkmaar.

\* Correspondence: h.j.kingma@mca.nl.

## Background

A dose-dependent side-effect of the intravascular administration of iodinated contrast media (ICM) is contrast induced nephropathy (CIN). CIN is defined as an increase in serum creatinine of  $\geq 25\%$  from baseline or  $\geq 44 \mu\text{mol/l}$  within 3 days after ICM administration, in absence of alternative aetiology. CIN can be associated with significant morbidity rates and accounts for up to 12% of cases of hospital-acquired acute renal failure. The incidence in out-hospital patients is not well known. We implemented a CIN prevention protocol including identification of high-risk individuals according to the Dutch Institute of Healthcare Improvement (CBO) and preventive hydration using a sodium hydrogen carbonate 1.4% infusion scheme. Patients at risk of developing CIN are sent to an outpatient clinic for consultation by a nephrologist and the determination of preventive measures. The aim of the study was to determine the incidence of CIN in out-hospital patients undergoing contrast enhanced CT after the introduction of preventive measures.

## Methods

Between 1 February and 1 November 2009 a prospective observational study was performed. All out-hospital patients  $\geq 18$  years undergoing a iodinated contrast-enhanced CT scan were asked for a blood sample  $\leq 7$  days before and 2-4 days after the CT scan. Patients were included when serum creatinine was established within this period. Patients on hemodialysis and clinical patients were excluded.

## Results

Within the nine month period 207 patients provided informed consent. In 148 patients serum creatinine was established  $\leq 7$  days before contrast administration and within 2-4 days afterwards. This was the eligible population. Of the eligible population 2 patients experienced CIN (1.4%; 95% CI 0-3,2%). 15 patients were identified as high risk patients and attended the CIN outpatient clinic. None of these 15 patients developed CIN. The 2 CIN patients did not attend the CIN outpatient clinic and did not receive preventive hydration. Based upon the risk stratification they were not at high risk to develop CIN. In both cases renal damage was reversible. Both patients developed micro-albuminuria after the CT scan.

## Conclusion

In the eligible population of 148 patients 2 cases of CIN were established. This corresponds with an incidence of 1.4%. The low incidence of CIN can probably be explained by the introduction of preventive measures to identify and pre-treat high risk patients.

Keywords: contrast-induced nephropathy – iodinated contrast media – out-hospital patients – risk classification – prevention



## Why do patients experience adverse drug events? A prospective cohort study of 603 hospitalised patients

Aileen B. Dequito <sup>a\*</sup>, Peter G.M. Mol <sup>b</sup>, Jasperien E. van Doormaal <sup>c</sup>, Rianne J. Zaal <sup>d</sup>, Patricia M.L.A. van den Bemt <sup>d</sup>, Flora M. Haaijer-Ruskamp <sup>b</sup> and Jos G.W. Kosterink <sup>a</sup>

<sup>a</sup> Department of Hospital and Clinical Pharmacy, University of Groningen, and University Medical Center Groningen. <sup>b</sup> Department of Clinical Pharmacology, University of Groningen and University Medical Center Groningen. <sup>c</sup> Department of Hospital Pharmacy, Martini Hospital, Groningen. <sup>d</sup> Department of Clinical Pharmacy, TweeSteden Hospital and St. Elisabeth Hospital, Tilburg. <sup>e</sup> Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht University. <sup>f</sup> Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam.

\* Correspondence: j.g.w.kosterink@apoth.umcg.nl.

### Background

Adverse drug events (ADEs) in hospitalized patients are common and remain a challenge to patient safety. They have significant health and economic impact; therefore, detection and prevention of ADEs should be improved by making use of several risk determinants. This study analyzed the prevalence of ADEs (preventable and non-preventable) in two Dutch hospitals based on the different risk determinants and identified the additional value of multimorbidity as determinant for ADEs.

### Methods

Adverse events experienced by patients admitted in the general internal medicine, gastroenterology, rheumatology and geriatric wards were prospectively identified through daily ward visits for six months after the implementation of a computerized prescribing order entry (CPOE) system. Causal relationship between adverse events and patients' drugs were assessed using Yale algorithm. Age, gender, number and type of drugs used, length of stay, hospital ward, Charlson score and multimorbidity were the risk determinants considered in this study.

### Results

In the study, 649 hospitalized patients were included wherein 349 (58%) experienced ADEs. Among the patients with ADEs, 307 (88%) had non-preventable ADEs (nADEs); 42 (12%) had preventable ADEs (pADEs) related to medication errors. Increasing morbidity ( $OR_{adj} = 1.28$ ; 95% CI 1.14-1.45), female gender ( $OR_{adj} = 1.77$ ; 95% CI 1.12-2.80), length of stay ( $OR_{adj} = 1.11$ ; 95% CI 1.07-1.16), increasing number of prescriptions ( $OR_{adj} = 1.13$ ; 95% CI 1.06-1.21), use of drugs affecting the nervous system ( $OR_{adj} = 1.83$ ; 95% CI 1.09-3.07) and admission to geriatric ward ( $OR_{adj} = 3.82$ ; 95% CI 1.73-8.45) significantly increased the risk of nADEs. Meanwhile, significant determinants for pADEs were multimorbidity ( $OR_{adj} = 1.84$ ; 95% CI 1.31-2.60), length of stay ( $OR_{adj} = 1.12$ ; 95% CI 1.03-1.21), number of prescriptions ( $OR_{adj} = 1.17$ ; 95% CI 1.05-1.31), Charlson score ( $OR_{adj} = 1.93$ ; 95% CI 1.20-3.11) and use of drugs affecting blood and blood forming organs ( $OR_{adj} = 10.35$ ;

95% CI 1.50-71.38). Multimorbidity was an important determinant for both nADEs and pADEs.

### Conclusion

In our study, half of the hospitalized patients experienced ADEs, of which only 12% were associated with transcribing or prescribing errors. Most interventions focus on medication errors to prevent ADEs, but majority of the ADEs (even after introduction of CPOE) is not preventable. Signaling early potential adverse events that occur during the normal use of drugs especially in multimorbid patients and subsequent therapeutic interventions may improve patient safety. Tools like clinical decision support may help identify such patients, but maybe even more important is establishing a strong patient safety culture supported throughout the hospital.

Keywords: adverse drug events – medication errors – clinical decision support – determinants

## Diversity of antibiotic use in neonatal intensive care units in the Netherlands

T.B.Y. Liem <sup>a\*</sup>, T.G. Krediet <sup>b</sup>, A. Fleer <sup>c</sup>, A.C.G. Egberts <sup>a</sup> and C.M.A. Rademaker <sup>a</sup>

<sup>a</sup> Department of Clinical Pharmacy; <sup>b</sup> Department of Neonatology; <sup>c</sup> Eijkman-Winkler Centre for Microbiology, Infectious Diseases and Inflammation; University Medical Centre Utrecht, Wilhelmina Children's Hospital, Utrecht.

\* Correspondence: y.liem@umcutrecht.nl.

### Background

Monitoring antibiotic use is essential to prevent overuse and misuse of antibiotics and to address the threat posed by resistant microorganisms. Studies have shown great variability in use of antibiotics between Dutch and European hospitals. Since empiric antibiotic therapy differs between NICUs and there is no consensus on the choice of antibiotics, we examined the diversity in antibiotic use in ten NICUs in the Netherlands in 2005.

### Methods

From all ten NICUs in the Netherlands we collected clinical and demographic characteristics and type and quantity of systemic antibiotic use (DDD/100 admissions, represented by the dispensing of antibiotics from the hospital pharmacies to the NICUs) in 2005 and local treatment guidelines on neonatal sepsis, meningitis and necrotizing enterocolitis (NEC). Antibiotics were ranked by volume of DDDs and those antibiotics that accounted for 90% of the total volume of use (DU90%) in each NICU.

### Results

Antibiotic consumption (based on pharmacy dispensing data) ranged from 130-360 DDD/100 admissions. In total 9-24 different antibiotics were used, of which 3-10 were in the DU90%-segment. Multivariate linear regression demonstrated that the differences in

total antibiotic use and in the DU90% segment were only weakly associated: 41% and 42%, respectively, with variation in demographic characteristics between the 10 NICUs (BW, GA, mortality, incidence of neonatal sepsis and length of stay). Antibiotic use according to the treatment guidelines in a particular NICU varied from 25% to 77%.

## Conclusions

By comparing antibiotic use in Dutch NICUs we found a considerable diversity in number of different antibiotics used, and total amount of antibiotic use, only weakly associated with differences in demographic data between NICUs. In addition, there was a wide variety in antibiotic use according to treatment guidelines. Further exploration of the opportunities to reach consensus in antibiotic policy and increased attention to antibiotic stewardship is recommended.

Keywords: antibiotic use – NICUs – neonates – diversity

## Pilot project on the development of a clinical prediction model for bleeding complications in hospitalized patients with coumarin therapy

A.D. Lindemans <sup>\*</sup>, P.M.L.A. van den Bemt and A.G. Vulto  
Erasmus University Medical Centre, Rotterdam.  
<sup>\*</sup> Correspondence: a.lindemans@erasmusmc.nl.

## Background

Epidemiological research has shown that in approximately 20% of hospital admissions an error or near miss has taken place. In 60% of these cases, medication is involved. In the Netherlands, it is estimated that each year 3000-6000 patients die because of errors and near misses, and probably half of these deaths are avoidable. Vitamin K antagonists (VKAs) are considered a high-risk medication for bleeding complications. If we could identify patients with a high risk for a bleeding complication in an early stage, it might be possible to prevent such bleeding complications. We propose to develop a clinical prediction model for the risk of bleeding complications in hospitalized patients on VKAs, using electronic patient data (EPD). This would enable hospital pharmacists to identify high-risk patients and provide them with specific medication advice which helps to limit adverse events and complications.

## Methods

Design: nested case-control research in a cohort of hospitalized patients using VKAs.

Cases: patients who have one of the following combined events:

- INR  $\geq 6$ ;
- INR  $\geq 6$  and vitamin K prescription;
- INR  $\geq 6$  and prothrombin complex (PCC) prescription;
- INR  $\geq 6$  and blood transfusion;
- INR  $\geq 6$  (immediately) followed by death.

Controls: patients on VKAs who do not have any of the above mentioned combined events.

Inclusion criteria: patients  $\geq 18$  yr, with a VKA prescription in the period 2006-2009.

Electronic patient records for extracting data on (a.o.) medication, clinical laboratory results, haematologic parameters (e.g. INR, PT), procedures/surgery, demographics, co-morbidity are used to collect patient data.

Result: risk factors for a major bleeding complication in hospitalized patients, incorporated in a clinical prediction model.

Analysis: logistic regression analysis for analysis of the case-control design. 'Backward' selection to select the strongest predictors in a multivariate regression model. The development process will be repeated in 'bootstrap samples' to determine the optimization of the model (internal validation).

## Results

The results presented here are raw data on the included population. In the four year period 2006-2009, 6328 patients have been prescribed a VKA. Of these, 2066 patients undergo 4885 events. Prescriptions of VKAs and vitamin K have been extracted from data from the computerized physician order entry system Medicator.

Event	# Patients (%)	# Events
Any	2066 (33)	4885
INR $\geq 6$	964 (15)	1943 <sup>a</sup>
Vitamin K <sup>†</sup>	816 (13)	1179 <sup>b</sup>
PCC	445 (7.0)	556 <sup>c</sup>
Blood transfusion	96 (1.5)	369 <sup>d</sup>
Death	968 (15)	968

<sup>†</sup>: Prescriptions vitamin K have been extracted from data from the computer physician order entry system Medicator, excluding prescriptions from the intensive care units, and the thoracic department.  
<sup>a</sup>: all INR measurements  $\geq 6$   
<sup>b</sup>: all vitamin K prescriptions, defined by unique date of prescription  
<sup>c</sup>: PCC, defined by unique date of administration  
<sup>d</sup>: blood transfusion days

## Conclusions

One third of the patients using VKAs undergo any event. A total of 964 patients (15%) have one or more INR  $\geq 6$ . The number of patients undergoing a combined event has not yet been established. Of all patients using VKAs, 15% might be at increased risk for a bleeding complication.

Keywords: coagulation – VKA – bleeding – risk factor – prediction model

$^{13}\text{C}$ -urea and  $^{15}\text{N}_2$ -urea: elegant markers to define location and kinetics of *in vivo* release from a colon-targeted delivery device in men

R.C.A. Schellekens<sup>a</sup>, G.G. Olsder<sup>a</sup>, J.M. Maurer<sup>a\*</sup>, J.G.W. Kosterink<sup>a</sup>, H.J. Woerdenbag<sup>c</sup>, K.D. Wutzke<sup>d</sup>, H.W. Frijlink<sup>c</sup> and F. Stellaard<sup>b</sup>

<sup>a</sup> Department of Hospital and Clinical Pharmacy, University Medical Center Groningen. <sup>b</sup> Laboratory Medicine, University Medical Center Groningen. <sup>c</sup> Department of Pharmaceutical Technology and Biopharmacy, University of Groningen. <sup>d</sup> Children's hospital, University of Rostock, Germany.

\* Correspondence: m.maurer@apoth.umcg.nl.

### Background

$^{13}\text{C}$ -urea and  $^{15}\text{N}_2$ -urea are expected to be suitable markers to assess the *in vivo* fate of colon-targeted dosage forms given by mouth. Release in the colon leads to fermentation of  $^{13}\text{C}$ -urea into  $^{13}\text{CO}_2$  and excretion of  $^{13}\text{CO}_2$  in breath, release in the small intestine to detection of  $^{13}\text{C}$ -urea in blood and urine.  $^{15}\text{N}_2$ -urea is excreted unchanged in blood and urine. The differential kinetics of  $^{13}\text{C}$ -urea in combination with  $^{15}\text{N}_2$ -urea can potentially describe both release kinetics and the gastrointestinal segment of release.

### Methods

Experiments were performed in healthy volunteers.  $^{13}\text{C}$ -urea was administered orally in a coated capsule designed for colon delivery or in an uncoated capsule. Also the use of a second, uncoated capsule filled with  $^{15}\text{N}_2$ -urea was investigated. The recovery of fermented  $^{13}\text{C}$ -urea was calculated from breath  $^{13}\text{C}$  enrichment, the recovery of absorbed  $^{13}\text{C}$ -urea from the  $^{13}\text{C}$  and  $^{15}\text{N}$  enrichments in blood and/or urine.

### Results

After intake of the colon delivery device, recoveries of  $^{13}\text{C}$  in breath  $\text{CO}_2$  and in blood as  $^{13}\text{C}$ -urea showed a high inverse correlation. Total recovery of  $^{13}\text{C}$  averaged >95%, indicating complete recovery.  $^{13}\text{CO}_2$  exhalation was observed in all subjects. The recovery of  $^{13}\text{C}$  in urine correlated well with that in blood. The ratio of recoveries in urine of  $^{13}\text{C}$  and  $^{15}\text{N}$  was identical (mean ratio 1.03) when  $^{13}\text{C}$ -urea is administered in uncoated capsules and <0.5 when administered in coated capsules. Kinetic parameters as lag time,  $t_{\text{max}}$  and pulse time could be derived from the time course of  $^{13}\text{C}$  enrichment in breath.

### Conclusions

$^{13}\text{C}$ -urea provides information on both the release kinetics of a colon-targeted oral dosage form and the gastrointestinal segment where it was released. With the simultaneous administration of  $^{13}\text{C}$ - and  $^{15}\text{N}_2$ -urea in combination with urine and breath sampling a non-invasive, single experiment, monitoring system of a colon-targeted delivery device has been developed.

Keywords: colon-targeting – urea-isotopes

Method for the development of national clinical rules

E. Meuwese<sup>\*</sup>, A.M. Scheepers-Hoeks, S.J.W. Wessels-Basten, H. Chao, E.W. Ackerman and R.J.E. Grouls

Department of Clinical Pharmacy, Catharina Hospital, Eindhoven.

\* Correspondence: anne-marie.scheepers-hoeks@catharina-ziekenhuis.nl.

### Background

The Catharina Hospital has developed several clinical rules for clinical decision support systems (CDSS) on regional scale and validated a method for this development [1, 2]. The aim of this study was to explore a method for the development of national clinical rules by cooperating with an expert team consisting of different specialties and settings.

### Methods

The national development was structured in a plan-do-check-act cycle (PDCA cycle), of which the check phase consisted of feedback by the national expert team. Beside different specialties and institutions, the editors of the guideline for the use of clozapine [3] (*ClozapinePlusWerkGroep; CPWG*) and the Special Interest Group Psychiatry (NVZA) were represented. Four PDCA cycles have taken place, in which the first check phase was a meeting, the second and third a correspondence by email and the fourth a plenary discussion with the CPWG.

### Results

Implementation of the existing guideline for the use of clozapine [3] in a clinical rule, warranted quantification of the various qualitative criteria and decision steps that are important during the use of clozapine. Therefore, extensive literature research and thorough discussion with the expert team was needed. After this, a complete overview of all possible electronic available information was formulated into a clinical rule (published at the website of the CPWG: [www.clozapinepluswerkgroep.nl](http://www.clozapinepluswerkgroep.nl)). The formulated PDCA cycle was supportive for an efficient and persistent development of the clinical rule, but several additional recommendations for this national approach are formulated:

- formulate a clear and complete goal, in which the framework of the national clinical rule is set down;
- use a structured method for the development of the national clinical rule, with regular evaluation of the process and the formulated goal;
- the expert team should:
  - be composed of experts that are competent and able to participate;
  - represent different specialties and settings;
  - represent relevant committees or workgroups;
- before initiating the development – or if needed during the development – establish criteria for:
  - feedback by the expert team;
  - decision-making;

- in case consensus is lacking, make a clear overview of the arguments and counter-arguments and relevant literature to guide the discussion.

### Conclusion

The national development of a clinical rule is labour-intensive, but can be well established with the described PDCA cycle and recommendations. The result of this development is national consensus about the content of the clinical rule. This can accelerate the national implementation, because the local implementation of the clinical rule then only requires the implementation and validation in a local CDSS.

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Keywords: clinical decision support system (CDSS) – national clinical rule – clozapine

### LC-MS/MS outperforms FPIA in monitoring everolimus therapy in renal transplantation

Dirk Jan A.R. Moes<sup>ab\*</sup>, Rogier R. Press<sup>ab</sup>, Johannes W. de Fijter<sup>b</sup>, Henk-Jan Guchelaar<sup>a</sup> and Jan den Hartigh<sup>a</sup>

<sup>a</sup> Department of Clinical Pharmacy and Toxicology; <sup>b</sup> Department of Nephrology; Leiden University Medical Center.

\* Correspondence: d.j.a.r.moes@lumc.nl.

### Background

There is a need to monitor everolimus blood concentrations (TDM) in renal transplant recipients, due to its high variability in pharmacokinetics and small therapeutic window. However, analytical methods to determine blood concentrations often differ in performance. Therefore, we investigated whether two commonly used TDM methods for everolimus were in agreement and to what extent their differences could lead to different dosage advices.

### Methods

612 whole blood samples were obtained from 28 adult renal transplant recipients receiving everolimus and prednisolone therapy. These samples included 287 everolimus trough concentrations. The remaining samples were obtained up to 6 hours post everolimus intake and allowed calculation of 84 AUCs<sub>0-12h</sub>. All samples were analyzed with fluorescence polarization immunoassay (FPIA) on an Abbott TDxFLx analyzer and LC-MS/MS.

### Results

Everolimus blood concentrations measured with FPIA and LC-MS/MS were not in agreement. Concentrations determined with FPIA were on average 23% higher than concentrations quantified with LC-MS/MS. Moreover, concentrations lower than 15 µg/L or AUC<sub>0-12h</sub> determined with FPIA could be 2-fold higher than with LC-MS/MS. When trough concentrations were measured with FPIA, higher inpatient variability was observed compared to LC-MS/MS. The overall variability in accuracy and precision can lead to clinically relevant differences in dose adjustment of up to 1.25 mg everolimus.

### Conclusion

LC-MS/MS outperforms FPIA for clinical drug monitoring and intervention of everolimus therapy in adult renal transplant recipients on dual therapy with prednisolone. Specifically the use of FPIA can lead to clinically relevant differences in everolimus dosage advices and higher inpatient variability.

Keywords: everolimus – renal transplantation – TDM

### Association between *HTR2C* gene polymorphisms and the metabolic syndrome in patients using antipsychotics: a replication study

Arne J. Risselada<sup>ab\*</sup>, Jelle Vehof<sup>fg</sup>, Richard Bruggeman<sup>f</sup>, Bob Wilffert<sup>e</sup>, Dan Cohen<sup>d</sup>, Asmar F. Al Hadithy<sup>eh</sup>, Johan Arends<sup>cd</sup> and Hans Mulder<sup>ab</sup>

<sup>a</sup> Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS). <sup>b</sup> Department of Clinical Pharmacy, Wilhelmina Hospital, Assen. <sup>c</sup> Mental Health Services Drenthe, Assen. <sup>d</sup> Mental Health Services GGZ-NHN, Heerhugowaard. <sup>e</sup> Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen. <sup>f</sup> Department of Psychiatry, University Medical Centre Groningen. <sup>g</sup> Department of Epidemiology, University Medical Centre Groningen. <sup>h</sup> Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam.

\* Correspondence: arne.risselada@wza.nl.

### Background

Two of our previous studies have investigated the possible association between the rs1414334 C/G and 759 C/T polymorphisms in the gene that encodes the 5HT<sub>2c</sub> receptor (*HTR2c*) and prevalence of the metabolic syndrome in a schizophrenic population. In both studies an association between the variant rs1414334 C-allele and increased prevalence of the metabolic syndrome was found. The objective of the current study was to try to replicate our previous findings in a different patient sample.

### Methods

Patients were included from an ongoing 'PHarmacotherapy Monitoring and Outcome Survey': PHAMOUS (www.phamous.eu). PHAMOUS combines a yearly somatic screening with routine outcome assessment in patients using antipsychotics. A cross-sectional

design was used to investigate the association between *HTR2C* variants and the metabolic syndrome in patients diagnosed with schizophrenia or related disorders. Patients,  $\geq 18$  years, were eligible for inclusion if they used antipsychotic drugs and gave informed consent. Primary endpoint was prevalence of the metabolic syndrome, as defined by the definition of the National Cholesterol Education Program's Adult Treatment panel III (NCEP:ATP IIIa). HbA<sub>1c</sub> was used when fasting glucose values were unavailable. Secondary endpoints were associations between *HTR2c* polymorphisms and individual parameters contributing to the metabolic syndrome, as well as effects of individual antipsychotics. Primary determinants were the 759 C/T and rs1414334:C>G polymorphisms in the X-linked *HTR2c* gene. The association between *HTR2C* genotypes (carriership of the variant *HTR2C* allele) and prevalence of the metabolic syndrome was investigated with logistic regression. Results were expressed as odds ratio's with a 95% confidence interval (95% CI). Data were investigated for potential confounding effects of age, ethnicity, DSM-IV diagnosis, gender, use of SSRIs and antipsychotic drugs.

## Results

In total, 186 patients, mainly male (68%) and Caucasian (93%), were included. Olanzapine (23%), risperidone (22%) and clozapine (17%) were the most frequently prescribed antipsychotic drugs. The variant rs1414334 C-allele was significantly associated with the metabolic syndrome (OR 3.99; 95% CI 1.40-11.33). There was a trend for an association between the variant rs1414334 C-allele and the metabolic syndrome in patients using risperidone (OR 16.50; 95% CI 0.73-375.43,  $p$  0.08). There was also a trend for an association between the variant rs1414334 C-allele and an increased risk for reaching the cut-off points for lowered HDL (OR 2.47; 95% CI 0.95-6.42) and elevated triglyceride levels (OR 2.21; 95% CI 0.94-5.18) respectively.

## Conclusions

This study confirms our previous findings that the variant C-allele of the rs1414334 polymorphism is associated with the metabolic syndrome.

Keywords: *HTR2C* – antipsychotics – metabolic syndrome – schizophrenia – rs1414334

## Optimizing phenytoin TDM using a clinical decision support system (CDSS)

J.S. Dral, A.M.J.W. Scheepers-Hoeks \*, E.W. Ackerman and R.J.E. Grouls

Department of Clinical Pharmacy, Catharina Hospital, Eindhoven.

\* Correspondence: anne-marie.scheepers@catharina-ziekenhuis.nl.

## Background

The use of anti-epileptic drugs (AEDs) is a prominent risk factor for

developing drug related adverse events [1]. One of the AEDs requiring therapeutic monitoring is phenytoin. Phenytoin induces several liver enzymes and reduces the serum concentration of many drugs while other drugs can influence phenytoin levels. In blood phenytoin is mainly bound to proteins and decreased protein binding can increase the free fraction substantially, resulting in toxic effects. A clinical rule guiding the monitoring of phenytoin therapy can assist the physician in improving patient safety. The aim was to develop a clinical rule for monitoring phenytoin therapy and investigate the potential impact of this rule on patient safety.

## Methods

The clinical rule was developed according to a plan-do-check-act cycle (Deming cycle) [2] and based on guidelines and literature [3, 4]. The clinical rule was retrospectively tested on patients admitted to our hospital in 2008 and 2009. Patient records were evaluated using the clinical decision support system (CDSS) Gaston (Medecs) and positive and negative predictive values (PPV; NPV) were calculated.

## Results

19 interactions expected to be of clinical significance ( $\geq 20\%$  change in serum concentration) and not covered by the G-Standaard were included in the clinical rule. Furthermore it is advised to determine free instead of total phenytoin when the ratio free/bound phenytoin is likely altered. 37,177 patients were admitted to our hospital during 2008 and 2009, 88 of them used phenytoin. In total 121 alerts were generated for 39 patients, 15 alerts resulted from incorrect CPOE use and 106 (87.6%) of the alerts were clinically justified. Interactions requiring phenytoin determination affected 18 patients. Phenytoin levels were spontaneously requested for five of them and all results were outside the therapeutic range. In 61% of the phenytoin TDM requests an altered free phenytoin fraction was likely.

## Conclusion

The alerts generated by the developed clinical rule can assist in improving patient safety through optimization of phenytoin TDM.

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Keywords: clinical rules – phenytoin – CDSS

## The impact of two manual medication cart filling methods on the frequency of medication administration errors: a prospective before and after study

Anneliene M. Schimmel<sup>ab</sup>, Matthijs L. Becker<sup>cd</sup>, Tilly van den Bout<sup>e</sup>, Katja Taxis<sup>f</sup> and Patricia M.L.A. van den Bemt<sup>g\*</sup>

<sup>a</sup> Faculty of Mathematics and Natural Sciences, University of Groningen.

<sup>b</sup> Department of Hospital Pharmacy, VU mc, Amsterdam. <sup>c</sup> Department of Hospital Pharmacy, Erasmus MC, Rotterdam. <sup>d</sup> Department of Epidemiology, Erasmus MC, Rotterdam. <sup>e</sup> Orthopaedic Ward, Erasmus MC, Rotterdam. <sup>f</sup> Section Pharmacotherapy and Pharmaceutical Care, University of Groningen. <sup>g</sup> Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University.

\* Correspondence: p.vandenbemt@erasmusmc.nl.

### Background

The distribution system used in a hospital influences the risk of medication administration errors. One aspect of the distribution system that may be important is the medication cart filling method. The medication cart can be filled using an automated system or a manual method and when using a manual method the medication can be arranged either by round time or by name. For the manual methods, it is hypothesized that the latter method would result in a lower frequency of medication administration errors, because nurses are forced to read the medication labels instead of administering all the medicines of one round without proper reading. Evidence on this hypothesis is lacking. Therefore, a study was designed to measure the effect of two manual medication cart filling methods on the frequency of medication administration errors.

### Methods

A prospective, observational study with a before-after design is set up, using disguised observation to detect medication administration errors. The medication cart filling method in usual care is to fill the cart with medication arranged by round time. The intervention is the implementation of the second medication cart filling method, where the medication cart is filled by arranging medicines by their names. The primary outcome is the frequency of medication administrations with one or more error(s) after the intervention compared with before the intervention. The secondary outcome is the frequency of subtypes of medication administration errors, namely omission of medication, unordered medication (including unauthorized medication), wrong preparation, wrong dosage form, wrong route of administration, wrong administration technique, wrong dosage and wrong time (at least 60 minutes too early/late).

### Results

After the intervention 170 of 740 (23.0%) medication administrations with one or more medication administration error(s) were observed compared to 114 of 589 (19.4%) before the intervention (odds ratio 1.24; 95% confidence interval 0.95-1.62). The distribution of subtypes of medication administration errors before and after the

intervention is statistically significantly different ( $p < 0.001$ ). Analysis of subtypes revealed more omissions (36.0%) and wrong time errors (39.4%) after the intervention than before the intervention (18.3% and 20.0% respectively). Unauthorized medication errors were detected more frequently before the intervention (17.5%) than after the intervention (4.0%).

### Conclusion

The frequency of medication administration errors with the medication cart filling method where the medication is arranged by name was not statistically significantly different from the frequency of administration errors with the medication cart filling method where the medication is arranged by round time.

Keywords: distribution system – manual medication cart filling method – medication administration error

## Clinical rule for drug dose adjustments in neonates and infants with renal impairment

Heleen van der Sijs<sup>\*</sup>, Dirk P. Boer, Lidwien M. Hanff and Eiske M. Dorresteijn

Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam.

\* Correspondence: i.vandersijs@erasmusmc.nl.

### Background

For estimating glomerular filtration rate (GFR) in children, the Schwartz formula is used:

$GFR (ml/min \text{ per } 1.73m^2) = 40 \times \text{height (cm)} / \text{serum creatinine } (\mu\text{mol/l})$

However, this formula is only valid for children aged >1 year.

Therefore, an alternative way needs to be developed to detect infants at risk of drug overdose because of renal impairment.

### Methods

Determination of reference values of enzymatically assayed serum creatinine in hospitalized children aged <1 year without known renal dysfunction. Premature neonates and neonates small for gestational age were excluded. Results were used to implement a clinical rule for paediatric ICU patients and corresponding dose guidelines.

### Results

Reference values for serum creatinine collected from 442 children aged 0-1 year show a rapid decline during the first two weeks of life, due to excretion of maternal creatinine, followed by a plateau and gradual rise afterwards, corresponding to the physiological maturation of renal function postnatally. No correlation was found between serum creatinine, and age, gender, height and weight. Therefore, a formula for calculating GFR in infants is not feasible. To develop a practical method to detect paediatric patients <1 year at risk, 4 creatinine cut-off points were determined for detection of renal impairment (3 cut-off points for the first month of life). A clinical rule was implemented using creatinine cut-off points in combina-

tion with a prescription of one of 45 selected renally excreted drugs. A list of selected patients at risk is sent daily to the pharmacy computer network. For children >1 year, the adult guidelines for dose frequency adjustments in renal impairment can be used after calculation of the GFR in ml/min per 1.73m<sup>2</sup> (formula of Schwartz). For children <1 year, the renal function can be estimated as a percentage by dividing the actual creatinine value to the age-dependent reference value. Assuming adults with a GFR have a 50% renal function, and a GFR of 30 ml/min corresponds to 30%, the guidelines for GFR-based dose frequency adjustments in adults are used in children < 1 year using the percentage renal function.

### Conclusion

Paediatric patients at risk of drug overdose in renal impairment can be detected using a clinical rule with age-dependent cut-off points. Normal dose adjustment guidelines for adults can be used after GFR calculation with the Schwartz formula (>1 year) or estimation of renal function percentage using a graph with reference creatinine values (<1 year).

Keywords: patient safety – drug therapy – computer assisted – clinical rule – renal impairment

## Effect of cytochrome P450 2C9 polymorphisms on dose and time to stable dose of sulfonylurea in primary care type 2 diabetes mellitus patients

J.J. Swen <sup>a\*</sup>, J.A.M. Wessels <sup>a</sup>, A. Krabben <sup>a</sup>, W.J. Assendelft <sup>b</sup> and H.-J. Guchelaar <sup>a</sup>

<sup>a</sup> Department of Clinical Pharmacy & Toxicology; <sup>b</sup> Department of Public Health and Primary Care; Leiden University Medical Center, Leiden.

\* Correspondence: j.j.swen@lumc.nl.

### Background

The CYP2C9 variant alleles CYP2C9\*2 and CYP2C9\*3 are associated with decreased sulfonylurea metabolism. However, most available data originate from pharmacokinetic analyses performed in healthy individuals. The aim of this study was to investigate the effect of CYP2C9\*2 and CYP2C9\*3 alleles on prescribed dose and time to stable dose of sulfonylurea in type 2 diabetes mellitus (T2DM) patients in a primary care setting.

### Methods

Incident sulfonylurea users with T2DM were recruited from four university-affiliated primary care centers. Retrospective clinical and prescription data were retrieved from the electronic patient record (EPR). Inclusion criteria were  $\geq 1$  prescription of tolbutamide, glibenclamide, glimepiride, or gliclazide after 1992,  $\geq 18$  years, no insulin use, and  $\geq 270$  days of follow up in the EPR. Primary endpoint was the stable sulfonylurea dose defined as the first period of  $\geq 270$  consecutive days without dose adjustment, initiation of other sulfonylurea, insulin or metformin. Secondary endpoint was the

time to stable dose. In a subset of the cohort the effect of the CYP2C9\*2 and CYP2C9\*3 allele on the change in fasting glucose levels was analyzed. The prescribed daily doses of the sulfonylurea were divided by the standard daily dose for each sulfonylureum derivative to allow combined analysis.

### Results

In total 207 patients were included. No statistically significant effect of the CYP2C9\*2 and CYP2C9\*3 alleles on the stable dose was found. However, a trend towards a lower stable dose for carriers of the CYP2C9\*3 allele compared to homozygous carriers of the CYP2C9\*1 allele was observed in the subgroup of patients treated with glimepiride (0.61 vs. 1.01,  $p = 0.07$ ). Of the patients, 152 (73.4%) achieved stable dose with a median time to stable dose of 59, 48, and 50 days for homozygous carriers of the CYP2C9\*1 allele, carriers of the CYP2C9\*2, and CYP2C9\*3 allele, respectively ( $p = 0.44$ ). For 75 stable patients (49.3%) fasting glucose levels were available. Levels decreased with 2.8, 2.6 and 2.4 mmol/L for homozygous carriers of the CYP2C9\*1 allele, carriers of the CYP2C9\*2, and CYP2C9\*3 allele, respectively ( $p = 0.89$ ).

### Conclusions

No significant effects of the CYP2C9\*2 and CYP2C9\*3 alleles were found on stable dose or time to stable dose, whereas carriers of a CYP2C9\*3 allele show a trend towards a lower stable glimepiride dose. Genotyping for the CYP2C9\*2 and CYP2C9\*3 allele appears to have no clinical implications for dosing of sulfonylurea in primary care patients with T2DM.

Keywords: pharmacogenetics – type 2 diabetes mellitus – CYP2C9 – sulfonylurea

## Unexpected high vancomycin levels; aberrant pharmacokinetics due to increased protein binding of vancomycin

J.W.F. Uges <sup>ab</sup>, M.J.T. Veuger <sup>c</sup>, P.W. Wijermans <sup>d</sup> and D.J. Touw <sup>ab</sup>

<sup>a</sup> Hospital Pharmacy; <sup>b</sup> Laboratory; Central Hospital Pharmacy, The Hague.

<sup>c</sup> Laboratory of Clinical Chemistry and Hematology; <sup>d</sup> Department of Hematology; Haga Teaching Hospital, The Hague.

\* Correspondence: j.uges@ahz.nl.

### Background

In our hospital all vancomycin therapies are subject to routine therapeutic drug monitoring. For selective patient groups pharmacokinetic population models are defined and in all individual patients these models are fitted to their sample results. However, in some cases measured levels do not match population pharmacokinetics. This case report describes a patient who developed extremely high vancomycin levels which could not be explained by sampling or dosage errors.

## Case

A 61-year old woman with a combination of multiple myeloma (free lambda-chains kappa/lambda 0.05) and Waldenström's disease (IgM kappa) was treated for progression of the Waldenström disease. Due to persisting fever a standardized antibiotic regimen of vancomycin (1000 mg/12 hr) and ceftazidim (1000 mg/8 hr) was started. During routine TDM peak and trough vancomycin levels were both >100 mg/l. As these levels were far outside our pharmacokinetic population models, sampling errors were suspected, therapy was continued and new blood samples were drawn. Despite good kidney function (serum creatinine concentration 36 µmol/l), the next day vancomycin peak level had risen to 330 mg/l. During the last vancomycin infusion minor neurotoxicity was observed. Pharmacokinetic analysis showed the following aberrant pharmacokinetic parameters (ref. normal population): total volume of distribution: 6.5 L (56 L) and vancomycin clearance of 0.15 L/h (6.4 L/h). Vancomycin therapy was immediately stopped and serum levels were monitored frequently. Sampling and dosing errors were ruled out. We hypothesized that due to high protein binding, specifically to monoclonal IgM, extravascular distribution was inhibited. This might result in high vancomycin serum levels, low distribution volume and reduced vancomycin clearance.

## Methods

To confirm altered pharmacokinetics the patient received a new 'therapeutic dose' of 100 mg vancomycin. Protein binding was analyzed by ultrafiltration. Also, in vitro binding studies were performed. For IgM purification a Hitrap IgM column was used where after IgM, vancomycin and albumin concentrations were measured in different fractions.

## Results

Pharmacokinetics remained the same after a new low dose. Regularly vancomycin binding to albumin and IgA is 30-55%. In this case over 98.5% of the vancomycin was bound. Free vancomycin was completely bound after mixing 'normal' vancomycin containing serum with this patients' serum. Vancomycin was still detectable (>2 mg/L) 2 months after therapy.

## Conclusion

During routinely TDM of vancomycin unexpected high vancomycin levels were observed. As dosing and sampling errors were ruled out, excessive protein binding was supposed. High protein binding of vancomycin, probably to the patients' monoclonal IgM, explained the high vancomycin levels, strongly decreased clearance and low volume of distribution.

An exploratory pharmacogenetic pathway approach to detect associations with adalimumab efficacy in rheumatoid arthritis

W.M. Kooloos<sup>a</sup>, J.A. Wessels<sup>a\*</sup>, R.J.H.M. van der Straaten<sup>a</sup>, J.H. Smit<sup>b</sup>, T.W.J. Huizinga<sup>c</sup> and H-J. Guchelaar<sup>a</sup>

<sup>a</sup> Clinical Pharmacy & Toxicology, Leiden University Medical Center. <sup>b</sup>

ApotheekZorg, Elsloo. <sup>c</sup> Rheumatology, Leiden University Medical Center.

\* Correspondence: j.a.m.wessels@lumc.nl.

## Background

The efficacy of anti-tumor necrosis factor adalimumab in patients with rheumatoid arthritis (RA) is about 60-70% and predictors for response are yet unknown. This study aims at exploring predictors for adalimumab efficacy in RA patients by associating response with polymorphisms in: 1) the pharmacological pathway of adalimumab, and 2) rheumatoid arthritis's disease susceptibility genes.

## Methods

In 325 RA patients treated with adalimumab, 223 polymorphisms in 111 genes were analyzed. Treatment outcome was evaluated after 3 months of therapy with the 28-joint disease activity score criteria (DAS28) using as the primary endpoint EULAR good response next to disease remission and relative change in DAS28 as secondary endpoints. Initially, polymorphisms were explored for associations under allelic and genotypic model using chi-square tests. Hereafter polymorphisms were tested in the best-fit genetic model meaning that either the Cochran-Armitage test for trend analysis or regression analyses under recessive or dominant models were applied. All analyses were adjusted for covariates age, gender, concomitant MTX therapy and DAS28 at baseline. Since this was an exploratory study, no adjustments for multiple testing were performed.

## Results

After 3 months of treatment with adalimumab, 174 (54%) and 103 (32%) of the patients responded according to the DAS28 good response and remission criteria. The average age at the start of adalimumab therapy was 56 years with a mean DAS28 at baseline of 5.9. In this cohort, 57 patients (18%) used adalimumab as monotherapy during evaluation period. Other patients received concomitant MTX with an average dose of 24.1 mg per week. Genetic analysis showed significant associations of 19 polymorphisms, 11 polymorphisms and 8 polymorphisms with good response, remission and relative change in DAS28, respectively ( $p < 0.05$ ). Four polymorphisms in CD40 ligand (*CD40LG*), vascular endothelial growth factor receptor 2 (*KDR*), TRAF family member-associated NFKB activator (*TANK*) and vascular endothelial growth factor A (*VEGFA*) were significantly associated with adalimumab response according to all endpoints ( $p < 0.05$ ). In addition, no consistent associations of 37 disease susceptibility polymorphisms and response to adalimumab were detected.



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## Conclusion

This study suggests that polymorphisms in genes coding for *CD40LG*, *KDR*, *TANK* and *VEGFA*, in the pharmacological pathway of adalimumab, are potential predictors for efficacy, whereas polymorphisms related to RA disease susceptibility show no consistent associations. These data provide new insights regarding the potential of pharmacogenetics related to adalimumab efficacy in RA.

Keywords: ti-tumor necrosis factor – pharmacogenetics – polymorphism – treatment outcome – rheumatoid arthritis