200 A note on the propensity score in observational studies of time-varying treatment with limited overlap

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Suissa, et al. (2017) proposed prevalent new-user cohort designs for a head-to-head comparison of drugs. In this design, patients receiving the comparator drug are matched to those receiving the newer drug based on time-conditional propensity scores of initiating the newer drug calculated within each exposure set (i.e. patient populations defined at each time point). The validity of propensity score matching generally relies on two assumptions (no unmeasured confounders and overlap/positivity), but the property of propensity score has not been established in studies of time-varying treatment with limited overlap. Here we show two theoretical properties. First, the propensity score for treatment at a specific time point is, as Rosenbaum and Rubin (1983) originally proved, the coarsest balancing score for the comparison of the two groups receiving the comparator drug and the newer drug at the time point, even after trimming patients in the regions of nonoverlap. Second, the set of propensity scores for treatment at different time points may be no longer a balancing score for the comparisons of groups receiving different sequences of treatment if we trim patients based on the set of propensity scores, which could depend on post-treatment variables. Numerical examples will be provided for illustration.

201 A methodological review of observational studies on psychotropic drug use in pregnancy and central nervous system outcomes in children

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Objective: Various epidemiological approaches have been used to study the association between psychotropic drug use in pregnancy and central nervous system (CNS) outcomes in children in the literature. This study aims to identify the methodological characteristics of existing studies in order to examine research gaps and recommend further research in this area.

Methods: A systematic literature search was conducted on observational studies in PubMed that studied psychotropic drug use in pregnancy and CNS outcomes in children up to 21 September 2017. Following independent screening and data extraction, a critical summary including the advancing trend of studies focusing on psychotropic drug use, differences between various data sources, methods to address bias and confounders, and the statistical analysis methods used was presented.

Results: 110 observational studies, 25 case-control studies, and 85 cohort studies were included in this review. Publications targeting antiepileptic drugs (AEDs) use dominated in the early years, but a gradual increase in research on antidepressants (ADs) in recent years contributed to the vast majority of relevant studies to date. No study about antipsychotics (APs) was identified in this review.

Conclusion: Evidence suggests that multiple factors, such as different study designs and data source choices, lead to inconsistent findings in the association between ADs and AEDs use in pregnancy and CNS outcome. Researchers should optimise study design including reasonable exposure period, data source, confounding adjustment methodology, as well as statistical analysis to minimise underlying bias for better precision, validity and generalisability of results.

202 The association between prenatal antipsychotics exposure and adverse obstetric and offspring outcomes: a systematic review and meta-analysis

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Aim: To evaluate the relationship between antipsychotics (APs) use in pregnancy and the obstetric and adverse offspring outcomes, in particular, pregnancy complications and congenital abnormalities, which could better comprehend the risk and address uncertainty in evidence-based guidelines and for future research.

Methods: A systematic literature search was conducted on observational studies in PubMed, EMBASE, PsycINFO and Cochrane Library that studied antipsychotics use in pregnancy and adverse obstetric and offspring outcomes up to 9 May 2018. Identified studies in the review will be included in meta-analysis when appropriate. Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality, while a quality rating of five or above was required for meta-analysis. Random-effect model with the corresponding 95% confidence interval (95% CI) was applied to pool the outcome results and heterogeneity among included studies was evaluated using I2.

Results: 11 cohort studies met the inclusion criteria with a total of 16,403 APs exposed pregnant women and 1,869,263 unexposed controls. Five studies obtained their data from population-based administrative databases/registries and six from ad hoc disease registries. With respect to maternal outcomes, the pooled estimates comparing prenatal APs exposure to non-exposure showed adjusted risk ratios (RRs) of 1.23 (95% CI: 0.99-1.54) in gestational diabetes, 1.02 (95% CI: 0.85-1.23) in pre-eclampsia/eclampsia, 1.07 (95% CI: 0.94-1.23) in cesarean section. While, adjusted RRs of 1.14 (95%CI: 0.94-1.38), 1.05 (95% CI: 0.87-1.27), 1.20 (95%CI: 0.93-1.55) and 0.94 (95% CI: 0.81-1.10) were estimated for congenital malformation, preterm delivery, small for gestational age, and large for gestational age, respectively.

Conclusion: Reviewed information was limited to define the safety of antipsychotics using in pregnancy. The results in this systematic review and meta-analysis do not support associations between maternal antipsychotic use and gestational diabetes, pre-eclampsia/eclampsia, cesarean section, congenital malformation, preterm delivery and small or large for gestational age.

203 The weight-losing effect of incretin-based therapies among type 2 diabetes: a systematic review and network meta-analysis

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Background: Incretin-based therapies, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and Glucagon-like peptide-1 receptor agonists (GLP-1RAs), have led to some unexpected effects during the long-term treatment on type 2 diabetes (T2DM), which may lead to further health problems and drug withdrawal. As have been reported, weight loss is one of the unexpected effects of incretin-based therapies.

Objective: We conducted a network meta-analysis to systematically evaluate the comparative weight-losing effect of incretin-based therapies in patients with type 2 diabetes (T2DM).

Method: PubMed, Embase, the Cochrane Library, ClinicalTrials.gov and related reviews were searched from inception to June 23rd, 2017 to identify randomized controlled trials (RCTs) concerning the weight-losing effect of DPP-4i or GLP-1RAs versus placebo or other anti-diabetic drugs in T2DM. Network meta-analysis within a Bayesian framework was performed to calculate the differences of mean weight before and after different drug therapies.

Result: 267 RCTs with 99,200 patients were included, comparing incretin-based therapies with other six classes of anti-diabetic drugs or placebo. The six antidiabetic drugs included alpha glucosidase inhibitor (aGlu), thiazolidinedione (TZD), sulfonylurea (SU), sodium-glucose co-transporter 2 inhibitor (SGLT2i), Metformin (Met) and insulin (INS). A statistically significant weight reduction was found in GLP-1 when compared with placebo(MD: 1.37, 95% CI: 1.05~1.69), aGlu(MD: 1.48, 95% CI: 0.56~2.40), TZD(MD: 3.63, 95%CI: 2.89~4.36), SU(MD: 3.40, 95% CI: 2.89~3.91) and INS(MD: 3.93, 95% CI: 3.48~4.37).Whereas, DPP-4i showed an natural effect when compared with placebo (MD:-0.31, 95% CI: -0.65~0.02) and aGlu (MD: -0.20 , 95%CI: -1.05~0.64)

Conclusion: Incretin-based therapies show significant effect on weight reduction in comparison with TZD, SU and INS. Also, GLP-1RA show a weight-losing effect compared with placebo and aGlu, while DPP-4I appears to have neutral effect when compared with placebo and aGlu.

204 Rates of all-cause community-acquired pneumonia among adult population in Taiwan

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Aim/Objective: Pneumonia is one of the leading causes of death for adult population in Taiwan. To reduce the clinical and economic impact of pneumonia, vaccination is considered as one of the effective approaches. However, due to the limited government budget, the allocation for vaccines is important. The objective of this study is to describe the rates of all-cause community-acquired pneumonia (CAP) among total adult population and patient subgroups with different risk.

Methods: This study was a retrospective study using Taiwan's national claims database. The study population comprised all persons ⩾20 year old in 2014 and was characterized in terms of the age group and the presence of underlying chronic medical conditions (risk profiles). Risk profiles were characterized based on medical information recorded during 2013. High-risk patients include patients with functional or anatomic asplenia, HIV infection, chronic renal failure, malignant neoplasm or solid organ transplantation, congenital immunodeficiency and diseases of white blood cells. At-risk patients include patients with chronic heart disease, chronic lung disease, asthma, diabetes, alcoholism, chronic liver disease, smokers, Down's syndrome and neuromuscular disorders. Persons without evidence of at-risk or high-risk conditions were classified as low-risk. All the information was derived in descriptive.

Results: The results showed that the rates of CAP increased with age and the rate was higher in at-risk population than those in high-risk and low-risk population. The study also found that CAP rate ratio (RR) among people with chronic lung disease (RR=19.66, 95% CI: 19.43-19.90) was highest compared to low-risk persons regardless of age, followed by people with disease of white blood cells (RR=15.37, 95% CI: 14.58-16.20) and people with chronic renal failure (RR=11.26, 95% CI: 10.96-11.56).

Conclusion: The rates of all-cause CAP among at-risk and high-risk populations were much higher than low-risk population, which has implications for future vaccination policy implementation.

205 Assessment of various risk factors of myocardial infarction in a tertiary care hospital in south India

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Aim/Objective: Risk factors for MI varies worldwide based on the geographical region, race, nutrition type etc. Understanding the risk factors in the local area is important to modify the risk factors in order to decrease the burden of MI locally, therefore the aim of the study is to assess the various risk factors of Myocardial infarction in a tertiary care hospital in South India.

Methods: This is a retrospective cross-sectional study were 560 patient's records from 2012 to 2015 were collected from September 2017 to March 2017. Details about their demography, risk factors were collected from the inpatient case records from Medical Records Department (MRD). SPSS software was used to do the descriptive analysis of the obtained data.

Results: A total of 19381 admissions were observed under cardiology department between 2012 to 2015, out of which 36.58% were due to MI. As per the study criteria a total of 560 MI cases were collected and analyzed for risk factors included in our study. Study showed male (74.6%) predominance over female (25.4%). The average age of study population was found to be 60.19±11.47 years and MI was found to be highest in the age group 46-65(59.80%) years. The most prevalent risk factor was found to be dyslipidemia (54.3%), followed by hypertension (53.45%), smoking (40.30%), Diabetes Mellitus (39.70%) and obesity (6.28%). Hypertension, diabetes and dyslipidemia were more prevalent risk factors observed in females compared to males and smoking (51.64%) had highest prevalence in males.

Conclusions: The study provides a valuable reference data on the distribution pattern of risk factors of myocardial infraction in south Indian patients. It also indicates the need for additional regional databases to broaden our understanding on how risk factors vary in different populations. Hence MI can be prevented by modifying the life style of population at risk.

206 Post-licensure surveillance of Human Papilloma Virus (HPV) vaccine using disproportionality analysis in Vaccine Adverse Event Reporting System (VAERS)

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Objectives: To identify the adverse events reported to VAERS database after HPV vaccination from July 2006 to May 2017 using disproportionality analysis.

Methods: A systematic data mining was performed in the VAERS database for reports associated with HPV vaccine, from July 2006 through May 2017. VAERS received 49444 reports associated with HPV vaccine within the aforementioned time period. Out of 49444, 2307 unique reactions, identified by removing the duplicates. Clinically relevant Vaccine Event Combinations (VEC) were identified in the VAERS database following HPV vaccination. We considered a VEC for analysis only if a minimum of hundred reports were present in the database for the given Adverse Event (AE). This resulted in fifty-seven clinically relevant VECs by omitting 2250 VECs as those had reports below hundred. The AEs associated with HPV vaccine which was detected earlier (clinical trials) and those mentioned in product label were excluded from analysis as the relation was already established. The data mining algorithm used for disproportionality analysis was Reporting Odds Ratio (ROR). A value of ROR-1.96SE >1 was considered as the positive signal.

Results: A total of 174 death reports and 3361 non-death serious reactions (Life threatening, hospitalized, prolonged hospitalization and disability) were reported to VAERS associated with HPV vaccine. 96.22% of reports were from the age group of 9-26 years. ROR showed positive signals for Anogenital warts (ROR-1.96SE=137.755), Cervical dysplasia (87.544), Amenorrhea (59.641), Syncope (15.149), Head injury (8.238), Alopecia (6.879), Loss of consciousness (6.791), Abortion spontaneous (5.509), Fall (4.735), Dizziness (3.192), Seizure (2.655), Migraine (2.388), Anemia (2.191) and Dyskinesia (2.176).

Conclusions: The present analysis showed fourteen potential adverse events associated with HPV vaccine. Although a causal relationship cannot be established, the number of cases reported suggest that there might be an association. Further studies are required to systematically validate the relationship.

207 A study to assess the impact of education on HPV Infection &Vaccination among parents by educating their adolescent girls

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Objective: To assess prevalence of HPV vaccination and to identify the impact of education in improving the knowledge and perception about the HPV infection and vaccination among the parents of adolescent girls.

Methodology: The prospective interventional study was conducted in four schools within a South Indian City, Mysuru. The informed consent form and the questionnaire were sent home with the identified adolescent girls. The signed informed consent and the questionnaire was collected back in the pre-interventional phase. Educational sessions were conducted for the students in their school and distributed an education leaflet to their parents. Three weeks later, questionnaires was re-administered to the parents via the enrolled girls and collected their response.

Results: A total of 403 parents consented for the study. The prevalence of HPV vaccination in the study population was 4.4%. There was a statistically significant improvement in knowledge in the post interventional phase of the study (p value 0.001), but couldn't identify a significant change in their perception (p value 0.479). Among the study population, fathers, participants from nuclear family and the parents whose children studying the syllabus of Indian certificate of secondary education (ICSE) showed better improvement in knowledge and perception. Parents belong to the socio economic class of upper middle and upper lower showed better improvement at the end of the study with a percentage of improvement of 58.93% and 48.44% respectively.

Conclusion: The study found an improvement in knowledge and perception of more than 40% in the post intervention phase irrespective of the socio economic back ground of the study population. Study proved that the health care professional can target school children to communicate effectively to their parents on importance of HPV vaccine as the study clearly observed a positive behavioral change among the study population.

208 Drug safety signal detection in regional healthcare database using the Tree-based Scan Statistic and its applicability in 4 settings

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Objectives: We aim to evaluate the performance of Tree-based Scan Statistic (TreeScan) under different settings for detecting statins-related adverse event in electronic healthcare database.

Methods: Patients older than 18 years old with hypertension in Yinzhou healthcare database from 2010 to 2016 were included in our study. The AEs were defined by using the ICD-10 codes of out/in-patient diagnosis. We established a set of reference signals to better evaluate the performance of the method. Our study compared the measures of the performance of TreeScan in 4 settings. In Poisson model, the patients with the indication of statin were served as background population. Under the new user cohort design, the statin initiators were identified by setting a washout period to exclude patients who took statins before. Propensity scores for statin use were then developed using logistic regression, statin initiators were matched 1:1 with non-users according to propensity scores with the nearest neighbor matching method.

Results: A total of 224,187 patients were finally enrolled and divided into two groups (85,758 statin users and 138,429 nonusers) in origin cohort. We identified 110,659 patients with dyslipidemia as background population in Poisson model. In new-user cohort, there are 21,551 statin users and 46,442 non-users. Baseline characteristics of two groups (19,819 patients in each group) were balanced after propensity score matching. In 4 settings, Poisson model generated fewest false positive and true positive signals with AUC that less than original data significantly. Compared to original cohort, all other indicators, including AUC (0.79, 95%CI: 0.66-0.93; 0.78, 95%CI: 0.64-0.92), were larger in new-user cohort and matched cohort, although the difference of AUC were not statistically significant.

Conclusion: TreeScan performs better in new-user cohort and matched cohort with fewer false positive signals and higher AUC.

209 GLP-1RAs and risk of diabetic retinopathy: analysis of the FDA Adverse Event Reporting System Database

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Objective: To assess the association between Glucagon-like peptide 1 receptor agonists (GLP1RA) and diabetic retinopathy (DR) using US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: DR events are defined as diabetic retinopathy, retinopathy, macular edema, "retinopathy proliferative" "retinopathy haemorrhagic" "blindness" "vitreous haemorrhage". By running a query on AERSMINE (an open access web data mining tool), we obtained the number of DR events and all other adverse events in GLP1RAs, each GLP1RA drug (exenatide, liraglutide, albiglutide, and dulaglutide) and all other (non-GLP1RA) drugs use from 2005 Q3 to 2017 Q3. We calculated proportional rate ratio (PRR) using 2 × 2 tables and 95% confidence interval (CI) and repeated analysis in patients with diabetes indication, patients without limiting indication, and patients with diabetes indication and without using insulin, respectively. We also downloaded the FAERS database and identified DR cases involved GLP1RA use up to 2017 Q3 by SAS software v9.4 (Cary, NC).

Results: A total of 267 GLP1RAs associated DR cases were extracted from FAERS, 175 cases involved exenatide and 64 cases involved liraglutide.In patients with diabetes indication, exenatide (2.52/1000p) had a PRR of 0.25 (95% CI 0.21-0.30; p<0.001), liraglutide (3.56/1000p) had a PRR of 0.41 (95% CI 0.32-0.52, P<0.001), albiglutide (1.58/1000p) had of PRR of 0.21 (95% CI 0.11-0.40, P<0.001), and dulaglutide (1.17/1000p) had a PRR of 0.17 (95%CI 0.08-0.33, P<0.001). In patients without limiting indication, the PRR of DR events for GLP1RAs was 0.7594 (95% CI 0.6768-0.8521, P<0.001); in patients with diabetes indication and without using insulin, the PRR is 0.3678 (95% CI 0.3053-0.4429, P<0.001). Overall, PRRs are consistent (PRR<1) across different population groups.

Conclusion: Our analysis indicated that there was no significant association between GLP1RA and DR. This study is limited by reporting bias and further studies are warranted to assess the potential DR risk of GLP1RAs.

210 Improvement of personal level identifiers is imperative in Japanese National Database: a research using claims data of corporate insurances

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Aim: No unique personal identifier like Social Security Number is available in Japan. Two types of identifiers (ID1 and ID2) are used in Japanese National Database (JNDB) made available for the research since 2011. ID1 is for the combination of [1] health card number (one for each household), [2] date of birth (DOB) and [3] sex. ID2 is for [1] name, [2] DOB and [3] sex. In a study using JNDB of 1-year period, one person had on average 1.2 ID1s and 1.4 ID2s assuming that ID1-ID2 pairs represented one person if either ID was the same (BMJ Open 2015;5:e006450). We examined the mechanisms of multiple ID2s and its impact on the research.

Method: We used claims data from 37 corporate health insurances collected between May 2010 and August 2017. ID1s and ID2s were generated for patients. The ethics committee in Nihon University School of Pharmacy approved the study.

Results: We found 3,792,478 ID1s and 5,588,940 ID2s (1.47 per ID1) in claims issued in electronic format where 3,503,752 ID1s (92.4%) and 4,767,026 ID2s (88.2%) were considered to represent 3,503,752 patients: [a] 2,240,478 with one ID1 and one ID2 and [b] 1,263,274 with one ID1 and two ID2s of patient names written in the different character types (Chinese vs. Katakana characters). Some of the remaining 288,726 ID1s (7.6%) with 2 or more ID2s represented twins of the same DOB/sex.

Conclusion: The main mechanism of multiple ID2s for one patient was that patient names could be written in either Chinese or Katakana character in Japanese claims. However, if pairs with the same ID1 were considered to represent one patient, twins are misclassified as one patient. The adoption of measures (e.g., the health card number for the individual) is imperative. In the future, the study on the mechanisms of multiple ID1s is warranted.

211 Multiple imputation of clinical variables in fee-for-service medicare population

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Objective: Trials suggest GLP1 analogues (GLP) may increase diabetic retinopathy (DR) risk. Assessing this signal in fee-for-service Medicare population (FFSMP) presents challenges due to lack of clinical detail. CPT II codes for clinical variables (CV) including A1c, blood pressure, and cholesterol provide confounding control, but are not reported for most patients. We assessed use of multiple imputation (MI) for available CV in an internal validation study to further balance cohorts to assess this risk.

Methods: We identified FFSMP initiating GLP or long acting insulin (LAI) between 2007-2015 excluding patients with blindness, low vision, or DR therapy, and defined DR by DR therapy procedure codes. We conducted MI using fully conditional specification with logistic regression for CV in arbitrary missing pattern allowing generalized logit model for nominal response data, then used propensity scores to balance confounders and estimated adjusted hazard ratios (aHR) using standardized mortality ratio-weighted Cox proportional hazards models censoring for treatment changes.

Results: A1c was available for 11% of GLP (n=11510) and 7% of LAI (n=110423) initiators. The prevalence of A1c category <7%, 7-9%, and >9% was 29%, 51%, and 20% in GLP and 23%, 44%, and 33% in LAI. The crude rates per 1,000 person-years were 3.4 (GLP) and 8.7 (LAI) over a median duration of 0.75 and 0.97 years, respectively. Comparing GLP to LAI, the aHR ignoring CV was 0.41 (0.29-0.59); when adjusting for imputed CV, the aHR was 0.45 (0.31-0.67), and was 0.57 (0.32-1.03) in patients with A1c ≤9%.

Conclusions: Among FFSMP who initiated GLP/LAI, ~7% have CV. Using MI to leverage this information moved the aHR slightly towards the null. Residual confounding is likely, due to the broad A1c categories, particularly in the highest A1c stratum. Identifying comparator drug classes with balance of CV may still be the most robust approach to controlling for diabetes severity.

212 Relationship of the potential companion diagnostic markers, BRM promoter insertion polymorphisms, and baseline cancer risk and prognosis

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Background: The SWI/SNF chromatin remodelling complex contains the ATP Brahma (BRM) subunit, inactivation of which promotes carcinogenesis. We identified two BRM promoter insertion-deletion polymorphisms that represses BRM gene expression, that can be reversed pharmacologically. As these drugs enter clinical trials, BRM polymorphisms may potentially serve as companion diagnostics. Before using these companion diagnostics for BRM-targeting agents, the association of these two BRM polymorphisms (BRM-741 and BRM-1321) with baseline cancer risk and outcome should be evaluated. Goals: Through a meta-analytic approach evaluating the role of BRM polymorphisms and either risk of prognosis of cancer patients.

Methods: A comprehensive online database search was performed using relevant keywords to identify studies based on a defined set of inclusion and exclusion criteria. Following this, the quality of these studies were assessed using Strengthening and reporting of genetic association studies (STREGA) modified guidelines. Required data was extracted from the selected papers and statistical analysis was performed on the same.

Results: In a meta-analysis of 9 publications, the double-homozygous insertion variants were associated with an increased risk of acquiring upper aero-digestive tumours (point estimates of BRM-741: OR=1.37, 95%CI:1.21-1.55,P<0.0001; BRM-1321:OR=1.62, 95%CI:1.34-1.97, P<0.0001; combined: OR=1.71,95%CI:1.31-1.22,P<0.0001). Sub-group analysis showed that the risks were mainly due to upper aerodigestive tract tumours (lung, head/neck, esophageal), and not in hepatocellular or pancreatic carcinomas. For prognosis, the homozygous insertion variants of BRM-741 HR=3.03,95%CI:1.95-4.70,P<0.0001 and BRM-1321 HR=2.91, 95%CI:1.93-4.41, P<0.0001 were individually associated with worse overall survival. Compared to patients carrying the double wild-type genotype, the double homozygotes variant were associated with worse overall survival (HR=4.75;95% CI:2.47-9.17; P< 0.00001).

Conclusion: BRM genetic polymorphisms have been shown to play a key role in the development and prognosis across multiple tumours. Because of the large magnitude of these prognostic associations of BRM polymorphisms, pharmacologic studies targeting BRM using polymorphic companion markers assessing response or efficacy must have a randomized non-treatment comparison arm.

213 The risk of mortality associated with haloperidol compared with other antipsychotics: propensity-score-matched cohort study in Hong Kong

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Aim: Numerous studies reported an increased mortality risk associated with haloperidol compared with other antipsychotics. However, limited studies used propensity score method to adjust for confounding and explored the mechanism underpinning the deaths due to the lack of information on death causes. This study aimed to investigate the risk of mortality and the specific causes of death associated with haloperidol versus other antipsychotics to address these limitations.

Methods: A cohort study was conducted using the data from Hong Kong Clinical Data Analysis and Report System. Patients with incident antipsychotic prescription (haloperidol, amisulpride, aripiprazole, chlorpromazine, olanzapine, quetiapine, risperidone, sulpiride, and trifluoperazine) in 2004-2014 were identified. Hazard ratios (HR) were estimated by comparing the risk of mortality for haloperidol with other individual antipsychotics using the Cox proportional hazards model stratified by propensity-score matched groups. Secondary analyses were conducted to further examine the specific causes of death including cardiovascular and pneumonia-related mortality.

Results: A total of 136,593 antipsychotic users were included. In a mean follow-up of 3.2 person-years, lower risk of all-cause mortality were found for all non-haloperidol antipsychotic drugs versus haloperidol, with HRs from 0.68(95% CI:0.64-0.72) for chlorpromazine to 0.43(95% CI:0.36-0.53) for trifluoperazine. Reduced risk of cardiovascular mortality were observed for risperidone (HR:0.79;95% CI:0.66-0.93]), sulpiride(HR:0.78;95% CI:0.64-0.96), chlorpromazine(HR:0.76;95% CI:0.65-0.90) and quetiapine (HR:0.67;95% CI:0.57-0.78). Lower risk of pneumonia-related mortality were observed for all non-haloperidol antipsychotics except amisulpride and olanzapine, with HRs from 0.76(95% CI:0.68-0.85) for risperidone to 0.38(95% CI:0.24-0.61) for trifluoperazine.

Conclusions: With robust control for confounding, haloperidol is found to be associated with an increased risk of mortality over other antipsychotics. The increased risk of cardiovascular and pneumonia-related mortality might account for some of the deaths associated with haloperidol. The cardiovascular and immunological profiles of the patients should be cautiously assessed before prescribing haloperidol. Other antipsychotics with lower observed risk could be considered as a preferred option.

214 The risk of cardiovascular events among antipsychotic-treated patients with schizophrenia in Japan

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Aim/Objective: To characterize the incidence of cardiovascular (CV) events among antipsychotic (AP)-treated patients with schizophrenia in Japan.

Methods: A retrospective cohort study based on the Japan Medical Data Center (JMDC) database evaluated the incidence of CV events among patients with schizophrenia treated with the following APs: the one-month long acting injectable (LAI) paliperidone palmitate (PP1M), other LAIs, or oral APs. Patients 20 to 75 years old with a diagnosis of schizophrenia were included in the analysis.

Results: Most patients were treated with oral APs (n=12,148) and there were limited data on the use of LAIs (PP1M: n=110; other LAIs: n=357). Compared to users of oral APs, users of PP1M and other LAIs were more often female (51.5%, 62.7%, and 65.8%, respectively) and had a history of hospitalizations in the prior year (11.1%, 45.5%, and 28.6%, respectively). PP1M patients had higher baseline Charlson comorbidity index (CCI) scores than patients treated with other LAIs and oral APs (mean CCI score: 0.82, 0.59, and 0.64, respectively). There were no CV events among patients treated with PP1M, and the incidence of CV events among users of other LAIs and oral APs was 0.55 and 0.44 per 100 patient-years, respectively. There were too few CV events in all AP exposure groups to conduct comparative adjusted analyses.

Conclusion: Among users of APs, there were limited numbers of CV events, which may be attributed to a potentially younger and healthier population of schizophrenia patients reflected in the JMDC database than in the overall population of schizophrenia patients in Japan. Users of PP1M had higher comorbidity at baseline compared to users of other LAIs and oral APs, which suggests the potential for channeling of PP1M. Research based on data from other sources is warranted to further understand the risk of CV events among AP-treated patients with schizophrenia in Japan.

215 Novel adverse events of iloperidone: A disproportionality analysis of US Food and Drug Administration Adverse Event Reporting System (FAERS) database

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Objective: To detect novel adverse events (AEs) of iloperidone by disproportionality analysis in FDA database of Adverse Event Reporting System (FAERS) using Data Mining Algorithms (DMAs).

Method: The FAERS database used in this study includes 1,96,10,041 Drug Event Combinations (DECs) which were reported from 2010 first quarter (Q1) to 2016 third quarter (Q3). Wherein, 1028 DECs were associated with iloperidone. We considered a DEC for disproportionality analysis only if a minimum of ten reports is present in the database for the given AEs. This resulted in 32 DECs by omitting 448 DECs as those had less than ten reports for iloperidone. The iloperidone associated AEs which were listed in product label and drug monograph were excluded from the study. This lead to 9 DECs out of 32. The most frequently used two DMAs, namely, Reporting Odds Ratio (ROR) and Information Component (IC) were applied retrospectively from 2010 (Q1) to 2016 (Q3) in FAERS Database. A value of ROR-1.96SE>1 and IC- 2SD>0 were considered as the threshold for the positive signal.

Result: The mean age of the patients of iloperidone associated events was found to be 44years [95% CI: 36-51], nevertheless age was not mentioned in twenty-one reports. The reports by gender were evenly distributed with a male to female ratio of 1.25:1, though gender was not revealed in 38 reports. The data mining algorithms exhibited positive signal for akathisia (ROR-1.96SE=43.15, IC-2SD=2.99), dyskinesia (21.24, 3.06), peripheral oedema (6.67,1.08), priapism (425.7,9.09) and sexual dysfunction (26.6-1.5) upon analysis as those were well above the pre-set threshold.

Conclusion: Iloperidone associated five potential signals were generated by data mining in the FDA AERS database. The result requires an integration of further clinical surveillance for the quantification and validation of possible risks for the AEs reported of iloperidone.

216 Analysis of eperisone induced adverse drug reactions using data from Korean pharmacovigilance system

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Aim/Objective: Eperisone is an oral muscle relaxant used in musculoskeletal disorders causing muscle spasm and pain. For more effective pain control, eperisone is usually prescribed together with nonsteroidal anti-inflammatory drugs (NSAIDs). As such, eperisone has been overlooked as the cause of adverse drug reaction (ADR) compared with NSAIDs. This study aimed to analyze the ADRs reported in Korea and suggest an appropriate diagnostic approach for eperisone-induced anaphylaxis.

Methods: We reviewed eperisone-related pharmacovigilance data reported in Korea from 2010 to 2015. ADRs with causal relationship were selected. Clinical manifestations, severity, outcomes, and re-exposure information were analyzed. For further investigation, 7-years ADR data reported in a single center were also reviewed. Oral provocation test (OPT), skin prick test (SPT), and basophil activation test (BAT) were performed in this center.

Results and Conclusion: During the study period, 207 patients had adverse reactions to eperisone. The most common ADRs were cutaneous manifestations (30.4%), followed by gastrointestinal symptoms (25.1%). There were 35 patients with anaphylaxis, comprising 16.9% of the total patient population. Thirty-five (16.9%) patients were re-exposed and symptoms were reproduced. In the single-center study, 37 patients were selected for analysis. Among them, 13 patients underwent OPT. All the provoked patients showed positive reaction. There were 11 patients with eperisone-induced anaphylaxis. Four of the 37 patients with anaphylaxis also underwent SPT and BAT, which were all negative. With these results, we concluded that eperisone can cause various ADRs, including anaphylaxis, possibly by inducing non-IgE-mediated immediate hypersensitivity.

217 Monitoring real world Prevenar 13 safety in China: a population-based cohort study with hybrid data collection methods and outcome validation

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Aim/Objective: To design an observational study to fulfill the Prevenar 13 key monitoring requirement of the China Food and Drug Administration.

Methods: A population-based electronic healthcare record (EHR) database in Yinzhou district of Ningbo City in China includes complete immunization records and healthcare data of all children in the district. Following a pilot study assessing the quality and completeness of Yinzhou EHR database, several different study designs were evaluated.

Results: A population-based cohort study with hybrid methods of primary and secondary data collections together with outcome validation is proposed to allow for most scientific rigor and data being collected in a rapid and time-efficient manner. The main study will utilize Yinzhou EHR database. Additionally, a validation study including a prospective cohort study in a sub-population of the main study and validation of International classification of diseases, tenth revision (ICD-10) codes for identifying all safety outcomes of interest (SOIs) will be conducted in order to offset the potential biased results from the main study because of potential misclassification of the SOIs due to miscoding and/or undercoding of ICD-10 codes used to identify the SOIs in the EHR database. The main study population consists of children aged 1-24 months receiving at least one dose of Prevenar 13 recorded in the EHR database between May 1st, 2017 and July 24th, 2020. The prospective cohort study includes children receiving the first dose of Prevenar 13 in the main study between July 1st, 2018 and July 24th, 2020. The main study and the prospective cohort study will evaluate the same SOIs.

Conclusion: As one of the first of its kind to utilize a population-based EHR database in China for the purpose of post-approval safety studies, the proposed study that aims to obtain high quality data is an effective and optimal option to expand the understanding of the safety profile of Prevenar 13 in Chinese children.

218 Feasibility assessment for an observational study evaluating effectiveness/safety of a fifth-generation cephalosporin antibiotic in community-acquired pneumonia (CAP) patients in China

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Aim/Objective: To determine the most feasible study design for a mandated observational study to evaluate effectiveness and safety of a fifth-generation cephalosporin antibiotic in CAP patients in China, where published pharmacoepidemiology studies are limited.

Methods: A hospital-based and database feasibility assessment was conducted from October – December 2017 in China. Hospitals were selected for outreach based on geography, size, and type to represent practice patterns variability. Suitable longitudinal databases were identified from a targeted search of peer-reviewed and grey literature.

Results: Twelve of 36 contacted hospitals (33%) completed feasibility survey (92% were university hospitals). Seven sites (58%) treated adults only, five (42%) treated adults and children. Ten sites (83%) treated inpatients and outpatients, one site treated inpatients only (8%), and one was unknown (8%). All sites had electronic records but some also supplemented with paper charts.

Median of 365 adults and 135 children per site were estimated to have been treated with intravenous cephalosporin antibiotics for CAP in 2016. Most patients were treated as inpatients (median: 200 inpatients, 140 outpatients) in a general ward, intensive care or other (median: 135, 55 and 65 patients). Median number of patients treated with second, third and other generation cephalosporins were 140, 250 and 80, respectively.

Demographics, medical history, CAP symptoms, laboratory/microbial tests, medications/ treatments, chest CT-scans, clinical response, safety events, and cause of death were indicated to be documented in medical records. CAP and safety event severity were less frequently documented. All hospitals indicated follow-up visits were routine; follow-up timing varied (1–4 weeks).

Four retrospective databases were evaluated; all had limited data on clinical response and treatment outcomes.

Conclusion: A retrospective cohort study involving medical chart review has optimal data availability/access, and is likely to be feasible to address objectives for mandated observational effectiveness and safety study in a CAP population in China.

219 Comparing the therapeutic role of antiviral ledipasvir/sofosbuvir versus interferon injections and protease inhibitors in the treatment of Hepatitis C

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Ledipasvir/sofosbuvir (Harvoni®) is a fixed-dose combination direct-acting antiviral used for the treatment and eradication of the Hepatitis C virus. This novel treatment is an alternative to the previously current standards of care which included interferon alfa-2a and protease inhibitors. As a result of high reports of positive patient outcomes, the cost of these potentially superior agents has become conceivably unaffordable. A systematic review was organized in order to evaluate the therapeutic role of the Gilead manufactured antiviral Harvoni and further to assess the effectiveness of this agent as a superior treatment for Hepatitis C to the alternative mainstay therapy of interferon alfa-2a and protease inhibitors. Literature searches of peer-reviewed and randomized controlled clinical trials testing the effectiveness of ledipasvir/sofosbuvir in the treatment for Hepatitis C was conducted, using MEDLINE and PubMed with publications between January 2013 and March 2018 in order to resolve the objective. The risk of bias was assessed regarding the sponsoring of the different studies and the involvement of Gilead manufacturers, as well as selective outcome reporting and other relevant biases, and further attenuated the inclusion criteria of this systematic review. Twelve studies were included in the review involving 2,639 participants in which their disease state of HCV varied from genotype, progression and virological HCV RNA levels. All twelve studies presented outcomes which indicated the effectiveness of ledipasvir/sofosbuvir as well as its superiority to previously used treatments which further bolstered claims of the drug's worth regarding inclusion on a formulary. Because of the burden of the Hepatitis C virus and the abundant reports of positive patient outcomes, it has been determined to be critical that health care institutions get access to affordable direct-acting antivirals, such as ledipasvir/sofosbuvir, in order to eliminate inferior therapeutic agents in the treatment of Hepatitis C virus.

220 Treatment adherence and factors affecting it in patients with stable angina pectoris during therapy with nicorandil

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Objective. To study an adherence to treatment and factors that affect it in patients with stable angina pectoris (SA) at the beginning of treatment and during long-term administration of nicorandil.

Material and methods. The study design is a prospective, observational and multicenter. Totally, 590 patients with SA were included: 261 (44,2%) females, 329 (55,8%) males. All patients, in addition to the standard antianginal treatment, were prescribed nicorandil 20 mg per day. For assessing levels of potential and actual adherence and factors, affecting them, original questionnaire was applied. After 1 and 3 months of follow-up, the data of 552 patients were collected. All these patients were divided into 3 groups, according to the adherence to nicorandil use during 3 months of observation (1) immediately refused to take the drug (n=150, non-adherent); (2) started, but then stopped taking nicorandil within this period (n=75, partially adherent); (3) taking nicorandil for all 3 months (n=327; adherent).

Results. Potentially adherents (intention to take nicorandil) were 582 out of 590 (98.6%) patients. Actually adherents were only 327 of 552 patients (59.2%). The main reason for immediately refusing nicorandil was polypharmacy (36% of all the reasons given). Discontinuation of nicorandil therapy within the first month of follow-up was more often due to adverse events (50% of all causes). Main reasons for termination of long-term therapy were polypharmacy (25% of all reasons) and lack of nicorandil effect (27%).

Conclusion. Levels of potential and actual adherence vary substantially. Factors related to the treatment adherence at the beginning of therapy and during long-term administration of nicorandil are also different. The leading cause of non-adherence at the start of therapy is polypharmacy; in later stages of treatment the leading causes of cessation of nicorandil therapy are side-effects and lack of efficacy.

221 Acarbose treatment and the risk of coronary heart disease in patients with type 2 diabetes: a cohort study

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Objective: To investigate whether acarbose treatment is associated with the potential benefits of coronary heart disease (CHD) in newly diagnosed patients with type 2 diabetes mellitus (T2DM) by using nationwide insurance claim dataset.

Methods: A retrospective cohort study was conducted by using the Beijing Urban Employee Basic Medical Insurance database during 2012-2015. A total of 1,627 newly onset T2DM patients without CHD were identified in 2012 and followed until the earliest of outcome occurrence, the latest medical record or study termination (December 31, 2015). The primary outcome was hospitalization due to CHD. Time-varying Cox proportional hazards regression was applied to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the association between acarbose treatment and incident of CHD, adjusted for patients' demographics, comorbidity, and co-medication. Subgroup analyses were performed based on the cumulative duration and dosage of acarbose.

Results: During 4 years of follow-up, the primary outcome occurred in 379 patients (47.55%) who had received acarbose treatment, as compared with 539 patients (64.94%) who never took acarbose therapy, which suggested that acarbose users group had lower risks of developing CHD (χ^2=49.99, P<0.05). By using those without exposure to acarbose as the reference group, acarbose users revealed neutral adjusted HR 1.07 (95% CI: 0.93, 1.22) for developing CHD. However, further analysis indicated that the adjusted HR (95% CI) was 2.08 (1.77, 2.45), 0.79 (0.65, 0.97) and 0.29 (0.22, 0.39) when the duration of taking acarbose was <60 days, 60-180 days and >180 days, respectively. Moreover, the adjusted HR was 2.02 (1.73, 2.37), 0.72 (0.58, 0.89) and 0.23 (0.17, 0.32) with acarbose cumulative doses <14,000 mg, 14,000-48,000 mg and >48,000 mg, respectively.

Conclusion: Newly diagnosed T2DM patients who used acarbose for a prolonged period or who reached certain amount of doses showed benefits on the development of coronary heart disease.

222 Comparison of medication strategy revise in newly-diagnosed type 2 diabetes patients using generics or brand-name acarbose

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Objective: To compare the medication strategy revise in newly-diagnosed type 2 diabetes patients using generics or brand-name acarbose in Beijing.

Methods: Retrospective cohort study was conducted using records of patients newly diagnosed with type 2 diabetes in 2012 in Beijing Urban Employee Basic Medical Insurance database (2012-2015). Based on the prescription of initial therapy, patients who used generic acarbose were divided into study group and those who used brand-name acarbose were into control group. Revised medication and length from initial therapy to revised therapy were described. Kaplan-Meier was used to compare revising rates between these two groups. Cox proportional hazards regression was applied to estimate the hazard ratio (HR) and 95% CI for the association of generic acarbose use and medication revise, adjusted for patients' demographics and comorbidity.

Results: 824 patients were included in the cohort. 121 patients (83.45%) in the study group and 460 patients (67.75%) in the control group revised medication. The median lengths of revising were 128 days in the study group and 175 days in the control group. Metformin was preferred when patients had to revise medication. The adjusted HR (95% CI) was 1.51 (1.23, 1.85).

Conclusion: Patients newly diagnosed with type 2 diabetes are more likely to revise medication when using generic acarbose as initial therapy.

223 Comparative effectiveness and safety of Ticagrelor versus Prasugrel following acute percutaneous coronary intervention

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Objectives: To evaluate the effectiveness and safety of ticagrelor compared to prasugrel in patients with an acute coronary syndrome (ACS) who underwent a percutaneous coronary intervention (PCI).

Methods: This retrospective, new-user design study included 3,666 commercial insurance beneficiaries who underwent ACS-related PCI from March 2012 through December 2014 captured within the Optum Clinformatics insurance database. All patients with claims for PCI occurring within 3 days of an ACS event were included if no history of coronary intervention and ticagrelor or prasugrel use in the previous 6 months. The primary endpoint, myocardial infarction, ischemic stroke, or all-cause death; and secondary endpoint, intracranial hemorrhage, gastrointestinal bleed, or other major bleed, were evaluated within one year. Cox proportional hazard models with inverse probability of treatment weighting were used to assess the risk of event occurrence between groups while adjusting for measured confounding factors including demographic characteristics, adherence, and other clinical variables.

Results: There were 1,070 patients initiated on ticagrelor and 2,596 initiated on prasugrel following incident PCI. Patients prescribed ticagrelor had slightly lower adherence than prasugrel users, as calculated by a ratio of medication days' supply and days of follow-up (T84.6% vs P87.4%; P<0.01). There were 189(17.7%) patients in the ticagrelor group and 446(17.4%) in the prasugrel group who experienced the primary endpoint during the study period (P=0.73). After adjusting for covariates, there was no difference in the primary endpoint (HR:1.0; 95% CI:0.81-1.2; P=0.94). For the secondary endpoint, 239(22.3%) new users of ticagrelor and 479(18.5%) new users of prasugrel experienced an event (P<0.01). A significantly lower risk of secondary endpoint occurrence was observed in the prasugrel group after multivariate adjustment (HR:0.76; 95%CI:0.64-0.92; P<0.01).

Conclusions: Among patients who underwent ACS-related PCI, prasugrel was associated with a decreased risk of bleeding events when compared to ticagrelor. Further investigation with a head-to-head RCT is required to fully evaluate the effectiveness and safety of ticagrelor and prasugrel.

224 Prevalence of adverse drug reactions of herbal medicines in Udupi region in Karnataka

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Introduction: Herbs have been used by man since ages for treatment of numerous illnesses. There is a great perception that herbal medicines of any kind are safe do not have any side effects. Among the herbal medicines, most common is Ayurveda. Even the ancient Ayurveda text books quotes that anything including medicines when irrationally used becomes a poison. Though Ayurveda, has been practiced since many years, the advent of technology and commercialization of medicines has caused a huge change in the entire system of practice.

Methods: An observational study was carried out among patients who are on Ayurveda medicines from different centers. Patients were followed up and observed for any kind of adverse drug reactions. Chronic patients were excluded from the study. ADR was tested using Naranjo algorithm for probability, Hartwigs scale for severity, Schumock and Thornton preventability scale for preventability.

Results: Total of 7 ADR were observed during the study. Out of 7 patients, 5 were female and 2 were male.
According to Naranjo scores, all ADR were rated as probable. Two out of 7 patients suffered from mild ADR, whereas others had moderately severe ADR. The results showed that around 6 out of 7 were preventable ADR.

Conclusion: The trend for pharmacovigilance in Ayurveda is changing. ADR cause a huge burden on patients. Most of the patients suffer from ADR which is preventable that has occurred due to irrational use of medicines, or self-prescription and many other factors. It is the need of the hour to control and document all these ADR pertaining to all forms of herbal medicines.

225 A review on methodological quality of current clinical trials of traditional Chinese medicine

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Objective: To figure out the RCTs proportion in the TCM clinical trials which were published in 2016 and to make an objective assessment of the methodological quality of the TCM RCTs using the CONSORT statement 2010 version as a guideline.

Methods: The keywords combined with “OR”,”AND” in two databases (CNKI and Pubmed) were used to search the articles from January 2016 to December 2016, which included traditional Chinese medicine, TCM, clinical trials and clinical study both in English and Chinese. We then selected the articles according to the inclusion criteria and exclusion criteria and assessed the quality of them according to the 10-item checklist of CONSORT statement 2010 version. This research also used the computer program called IBM SPSS Statistics 22 to do the statistical analyses part.

Results: A total of 210 TCM clinical trials were identified and 158 (88.78%) RCTs were included, of which 42 were from CNKI and 116 were from Pubmed. On average, 77.85% of the items on the checklist were provided for all the trials which were included. This is an obvious improvement compared with the reported ratio 62.9% in 2006 (checked using a 10-item checklist). Items including participants, interventions, objectives, outcomes were fully met while other items including randomization sequence generation, implementation and statistical methods, remained partially met. In particular, the sample size, the allocation concealment and the blinding/masking were disappointing. For instance, only 44.94% of RCTs followed blinding principle. Besides, the quality of TCM RCTs which were published on foreign journals was much higher than those published on Chinese journals.

Conclusion: Although the quality has been improved rapidly in the recent ten years, some methodology issues warrant closer examination. In particular, sample size calculation, allocation concealment and blinding should be carefully carried out to ensure the validity of TCM clinical trials.

226 An analysis of the cognitive status of ADRs in China and the best way to educate patients about ADRs

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Objective: To assess the cognition of Chinese people to adverse drug reactions (ADRs) and to evaluate the best way to educate patients about ADRs.

Methods: A cross-sectional self-administered survey was conducted during February 2018 to May 2018 by paper questionnaire and network questionnaire. The study was implemented in two settings in Shanghai: hospitals and public areas. The content of the questionnaire contains four aspects, basic information, cognition of ADRs, access to ADRs knowledge and patient's preference when they are instructed on ADRs.

Results: A total of 295 people filled out questionnaires, 56 of whom did not know what the ADRs was. Ten percent never read the drug instructions. On the contrary, the other 32.64% read every medication label carefully. 31.8% of people think that the more adverse reactions listed in the specifications of a drug, the more insecure the drug is. At the same time, 30.13% of people think that if the adverse reaction in the drug description is undefined, then the drug is considered safe (for example, some traditional Chinese medicine). 4.4% of people believe that they do not need to know the ADRs information. However, it is precisely this part of the population is most in need of being educated because of low level of culture and know nothing of ADRs. As for how pharmacists should explain the content of adverse reactions, 45.4% of people think that it is best to give a brief explanation of the ADRs information, and then answer the patient's questions in detail when necessary.

Conclusions: The incorrect opinion of the patient on adverse reactions needs to be corrected. The pharmacist needs to briefly introduce the most important and most common adverse reactions when dispensing drugs. Patients should be educated on how to deal with adverse reactions when experiencing it.

227 Predicting the severity of adverse drug reactions - the role of data mining

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Objective: Danhong Injection (DHI) is a compound preparation extracted from Danshen and safflower. It mainly treats coronary heart disease, angina pectoris, sputum-type pulmonary heart disease, and ischemic encephalopathy. This article has statistically analyzed the reports of 996 cases of adverse reactions/incidents of DHI received by spontaneous report system in a province in the past 10 years, and summarized the precautions, which could provide a reference for clinically safer and more rational use of DHI.

Methods: This study conducted a descriptive analysis of the reported patient's basic conditions and adverse reactions; using SPSS Modeler software, selected the risk factors affecting the extent of adverse reactions; based on SPSS Modeler software to establish risk models and the degree of adverse reactions to establish prediction models, and compare the prediction accuracy of each model.

Results: 1.Of the 996 cases of adverse reactions reported, 49.9% of cases reported cutaneous symptoms such as rashes and pruritus, 24.3% had circulatory symptoms such as palpitations, congestion and edema, and 13.8% had fever, chills and other symptoms.2.Risk factors affecting the severity of ADR include the number of pre-existing diseases, the number of combined medications, age, respiratory diseases, cardiovascular system diseases, circulatory system diseases, bone and joint diseases, thromboembolic diseases, brain and cerebrovascular diseases.. SPSS Modeler software selected Logistic regression and Bayesian networks to analyze the ADR severity and risk factors according to the data types. 3.After analyzing the two models of Logistic regression and Bayesian network, the accuracy of the two predictions was: 90.58% for training set, 93.07% for test set, 85.86% for validation set, 91.58% for training set, 91.09% for test set, and 80.81% validation set.

Conclusion: The model established by data mining technology can predict the severity of ADR in DHI. According to the research data, Logistic regression model is more suitable for predicting adverse reactions of DHI

228 Adverse effects of pharmacotherapy and treatment adherence in patients of the Profile outpatient register

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Aim. To analyze the adverse events (AEs) of pharmacotherapy and treatment adherence, and their relationship in patients of the outpatient register.

Materials and methods. The "Profile" outpatient register is a register of a specialised cardiology unit of the research centre. Data of 1531 patients were collected for period from January 2011 to 31 August 2015. There were two sources of information about AEs (1) data from outpatient register cards, filled in by physicians; (2) data from original questionnaires, filled in by patients. Treatment adherence was assessed by the 4-items Morisky Medication Adherence Scale (MMAS-4).

Results: AEs were recorded in 223 (14.6%) patients' cards, with a total of 301 adverse reactions. For the results of the questionnaires, 115 patients reported about of 139 cases of AEs. Various allergic reactions and symptoms of gastrointestinal disorders (pain, nausea, vomiting, diarrhoea, etc.) were leaders in the structure of AEs as in cards' records and in questionnaires' data either. Complete coincidence of information about AEs from the data of registration cards and questionnaires was found only in 46 patients. For the MMAS-4 results 108 patients (24.3%) were adherent to therapy, 121 (27.2%) patients were partially adherent, and 216 (48.5%) were non-adherent. AEs were more common in non-adherent patients ($p = 0.005$).

Conclusion: the results of the study demonstrated a similar structure of AEs pharmacotherapy according to the data of physicians (outpatient register cards) and patients (original questionnaires), but there was a much smaller number of AEs based on the results of the questionnaires. The null hypothesis on the relationship between AEs and adherence to therapy has been confirmed: patients with AEs of cardiovascular pharmacotherapy were more often non-adherent to the prescribed drug treatment.

229 DPP4i and risk of inflammatory bowel disease: analysis of the FDA Adverse Event Reporting System

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Objective: A recent cohort study indicated that dipeptidyl peptidase 4 inhibitors (DPP4i) were associated with increased risk of inflammatory bowel disease (IBD) in patients with type 2 diabetes. We thus performed this study to assess IBD risk among DPP4i users.

Methods: We downloaded the US Food and Drug Administration Adverse Event Reporting System (FAERS) dataset and performed analysis by SAS 9.4. To reduce confounding, we used second-line therapeutic alternatives including sulfonylurea (glimepiride, glyburide) and thiazolidinedione (pioglitazone, rosiglitazone) as control drugs, and selected control events that had a similar reporting rate to DPP4i among control drugs including chest pain, constipation, dyspepsia, syncope, and seizure. IBD cases, control events, and drug users were identified by search terms. The primary outcome was IBD events among DPP4i users; secondary outcomes assessed Crohn's disease and ulcerative colitis as individual endpoints. We estimated reported odds ratios (RORs) and 95% confidence interval (CI) for IBD between DPP4i and controls. We also performed a variety of sensitivity analyses to test the robustness of our results.

Results: We identified 86 IBD cases among DPP4i users and 219 IBD cases in users of the control drugs. Compared with control drugs, DPP4i had an ROR of 1.58 (95% CI 1.23-2.03) for IBD events, an ROR of 1.81 (1.27-2.58) for Crohn's disease, and an ROR of 1.43 (0.98-2.07) for ulcerative colitis. Sensitivity analysis showed an ROR of 2.74 (1.49-5.03) for IBD events reported as primary suspect, and an ROR of 1.96 (1.30-2.94) for IBD in patients not exposed to IBD-related treatments.

Conclusion: This pharmacovigilance analysis based on FAERS database indicated a signal for increased reported risk of IBD among DPP4i users compared to patients on therapeutic alternatives. However, as FAERS is prone to reporting bias, well-designed observational studies are needed to assess the risk of this rare event.

230 Attitudes and perceptions towards hypoglycaemia in patients with diabetes mellitus: a multinational cross-sectional study

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Aims: to explore hypoglycaemia problem-solving ability of patients who have diabetes mellitus and factors which determine their attitudes and perceptions towards their previous events.

Methods: a cross-sectional study was conducted in three Arab countries (Jordan, Saudi Arabia, and Kuwait) in patients with type 1 and type 2 diabetes mellitus, who are under antidiabetic therapy and have experienced hypoglycaemic events defined as self-reported event or event that led to admission in the past 6 months, for the duration between October 2017 and May 2018. The Hypoglycaemia Problem-Solving questionnaire was used in this study. This questionnaire contains two subscales; problem orientation (6-questions) and problem-solving skills (18-questions), using 5-point Likert scale that ranged from 0 to 4. Multiple linear regression analysis was used to identify predictors of hypoglycaemia problem-solving abilities.

Results: a total of 895 patients have participated in this study from the three countries (300 from Jordan, 302 from Saudi Arabia, and 293 from Kuwait). The mean patient age was 53.5 (SD= 13.7) years, of which 52.4% (n= 469) were males. Around 10.4% (n= 93) of the patients had a previous history of severe hypoglycaemia that lead to admission during the past 6 months. Patients had moderate overall problem-solving ability with an average score of 60.09 (SD= 13.05). Patients had better problem-solving skills compared to problem-orientation skills. Highest sub-scale score was for evaluating strategies with 2.92 ± 0.87. The lowest sub-scale score was for immediate management with 1.86 ± 0.99. Older age, being educated, married, having T2DM, on insulin therapy, and not admitted for hypoglycaemia were important predictors of patients problem-solving ability ($p<0.05$).

Conclusions: Healthcare professionals must educate patients more on how to self-manage their hypoglycaemic events; specifically they should focus on the overall problem-solving perception of hypoglycaemia, and its immediate management.

231 Clinical features of drug-induced liver injury: a systematic analysis of the Chinese literature including 15336 patients

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Objective: To investigate the clinical features of drug-induced liver injury, and know the epidemiological features of DILI in China.

Methods: Related database were searched for original literature on DILI in China published from January 2014 to March 2018, and a total of 90 articles with 15336 DILI patients were included in this analysis. Data on the gender, age, basic liver disease, alcoholic history, types of drugs, ways of medication, clinical classifications, occurrence time, clinical manifestation and prognosis of DILI were extracted and analyzed.

Results: As 15336 cases recorded gender in 90 articles recorded information, there were 7510 (48,97%) male and 7826 (51.03%) female. The average age was 47.7 years old, and 40～59 years old accounted for the largest proportion. The six most common causative drugs were traditional Chinese medicine (34.36%), anti-microbial drugs (12.06%), anti-tubercular agents (11.50%), antineoplastics (10.06%), Cardiovascular system drugs (6.11%), analgesic-antipyretic (4.66%). The ways of medication mainly were oral medication (60.04%) and intravenous medication (32.28%). 60.28% were classified to hepatocellular type, 21.05% cases were cholestasis type and 28.67% were mixed type. 71.57% DILI occurrence time were between 5days and 90 days. The main manifestation were fatigue (53.62%), poor appetite (44.84%), jaundice (38.96%). As for the prognosis, 33.25% cases cured, 55.22% cases improved well, 0.91% worse to death.

Conclusion: Females were slightly more than males about the rate of DILI. traditional Chinese medicine is the most common causative drugs for DILI. The hepatocellular type is the most common clinical type. Most patients have good prognosis.

232 Epidemiology of delayed onset hypersensitivity reactions after administration of low osmolar iodinated contrast media

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Background: The delayed hypersensitivity reactions of the iodide contrast media (ICM) are difficult to diagnose because of considerable time lag between ICM administration and symptom development. Therefore, epidemiologic studies on delayed hypersensitivity reactions are still insufficient to characterize precise incidence and risk factors. The aim of this study was to evaluate the incidence and risk factors of delayed hypersensitivity after administration of widely using non-ionic low osmolar contrast media (LOCM).

Methods: Patients using LOCM were monitored for 4 weeks in a single institution. Informed consent was obtained before monitoring. Seven days after the use of LOCM for each patient, the occurrence of symptoms, onset time, and duration of adverse events were inquired by text message first and telephone for nonresponsders. All the response was analyzed in relation to LOCM types and clinical characteristics.

Results: A total of 8,245 patients used one of five kinds LOCM (iobitridol, iohexol, iomeprol, iopamidol, and ioversol) for 4 weeks, of which 450 patinets (5.45%) had adverse reactions. While immediate hypersensitivity reactions were reported in 126 (1.53%), delayed hypersensitivity reactions were monitored in 324 (3.93%) during the same period. On the average, delayed hypersensitivity by LOCM occurred after 3 days and lasted for 5 days and 73.6% of affected patients had skin reactions. The severity of delayed hypersensitivity reaction was mostly mild (61.7%) or moderate (33.0%). The frequency of delayed hypersensitivity reactions varied from 2.5% (iopamidol) to 6.8% (ioversol) according to the subtypes within LOCM class. The severity of delayed hypersensitivity also differed by LOCM subtypes. Among the patients with delayed hypersensitivity, the proportion of moderate reaction was varied from 28.1% (iobitridol) to 51.6% (iomeprol).

Conclusion: Delayed hypersensitivity reactions of LOCM occur about 2.6 times more frequently than immediate type. While the onset of delayed reactions was not different according to LOCM types, incidence and severity were different by subtypes of LOCM.

233 Breastfed infants' adverse reactions caused by drugs in milk: an analysis of case reports in China from 1974 to 2017

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Aim: Some particular drugs can cause adverse reactions in breastfed infants via milk, but the comprehensive knowledge is still obscure, especially in Chinese infants. The aim of this study was to analyze the breastfed infants' adverse drug reaction via drug in breastmilk from cases report in Chinese database.

Methods: Literatures were retrieved in CNKI, VIP, WanFang Data, SinoMed and Baidu Scholar (date to 2017/12), clinical features extracted from case reports and articles related breastfed infants' adverse reactions were analyzed, Naranjo Algorithm was used to estimate the probability of adverse reactions caused by drugs.

Results: Excluding irrelevant and repeated literatures, 97 cases in 67 literatures was included, involving 49 males, 35 females and 13 infants with unknown gender. 68.1% (66 cases) adverse reactions was observed in 0～6 month infants, 21.6% (21 cases) in 7～12 month infants, 9.3% (9 cases) in infants order than 12 month and 1 infant's age was unknown. The top three drug classes causing adverse reactions via milk were antimicrobial agents (22.7%, 22 cases), oral contraceptives (14.4%,14 cases) and nervous system drugs (8.2%, 8 cases) respectively. The first three type of adverse reactions were skin and subcutaneous tissue disorders (32.0%, 31 cases), blood disorders (15.5%, 15 cases) and nervous system disorders (14.4%, 14 cases) respectively. 49.5% (48) of the cases were rated "probable" and 50.5% (49) were rated "possible" by using the Naranjo Algorithm.

Conclusions: The infants with lower month of age were more likely to be affected by the drug in mother's breastmilk, it should pay more attention in pharmaceutical service for lactating women.

234 Impact of medical conditions and medication use during pregnancy on adverse birth outcomes: a hospital-based case-control study

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Objective: To identify the impact of medical conditions and medication use during pregnancy on the development of adverse birth outcomes (ABO) among neonates.

Methods: A case-control study was carried out in a tertiary care hospital over a period of three years. All the live born and stillborn (≥20 weeks of gestation) neonates were included and categorized into cases and controls based on the presence or absence of any ABO, respectively. Demographic details, medical and medication history of mothers of the neonates included in study were collected. Binary logistic regression analysis was carried out to identify the risk factors for ABO.

Results: A total of 1214 neonates and their mothers (1180) were included in the study, out of which 556 (45.8%) neonates were found to have at least one ABO. Physical abnormalities to hips & genitalia (18), head & neck (16), skin (12) and low birth weight (320), pre-term birth (256) and respiratory distress syndrome (50) were the major ABO observed among neonates. Hypertension (11.2%) was the majorly seen medical condition among mothers, followed by hypothyroidism (8.3%) and diabetes (7.8%). Thyroxine supplements (7.6%), calcium channel blockers like nifedipine and nicardipine (7.1%), labetalol (4.7%), magnesium sulphate (3.4%) and insulin (2.2%) were the most common medications used by mothers during their current pregnancy. After adjusting for demographics, other medical conditions and medications, it was found that hypertension (OR=4.59), oligohydramnios (OR=8.51), use of labetalol (OR=6.21), magnesium sulphate (OR=12.02), methyldopa (OR=11.62), nifedipine (OR=4.83) and nicardipine (OR=11.63) were the risk factors for ABO.

Conclusion: The overall prevalence ABO among neonates, medical conditions and their medication use among pregnant women was found to be higher compared to western studies. Hypertension and their medications were found to be the major risk factors for ABO.

235 Factors affecting ototoxicity in head and neck squamous cell carcinoma (HNSCC) patients treated curatively with cisplatin-based chemoradiation

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Aim: Hearing loss is a long term, permanent toxicity associated with cisplatin use and radiation to the head and neck. There are no universal recommendations regarding baseline or follow-up hearing testing in HNSCC patients treated with cisplatin-based chemoradiation.

Methods: At Princess Margaret Cancer Centre, a prospective observational study assessed HNSCC patients receiving curative-intent and post-operative cisplatin-based chemoradiation. Hearing tests were performed at baseline and follow-up (0.7-18.5 months after initiation of first chemotherapy cycle) at physician's discretion. Significant ototoxicity was defined as ≥grade 2 audiometric change from baseline to post-treatment (CTCAE v.4.02) in one or both ears.

Results: Of 642 eligible patients (years 2008-2015) enrolled, 549 received definitive chemoradiation and 93 received post-operative chemoradiation. Median age was 57.5 years; 114 (18) were female; 421 (66%) were from the oropharyngeal site (OPC); 105 (16%) were from oral cavity (OC); 56 (9%) were from laryngeal site; 34 (5%) from hypopharyngeal site; and 26 (4%) had an unknown primary treated as HNSCC. 576 (90%) were Stage IV. Only 246 patients received both baseline and follow-up hearing tests, of which 142 (22% of 642) met the definition of significant ototoxicity (94 bilateral/48 unilateral loss). None had received prolonged courses of other ototoxic agents to explain hearing loss. Hearing loss was significantly higher (each $p<0.001$) for OPCs (27% of 421) when compared to all others (13% of 221); for high-dose (24% of 557) vs. low-dose weekly cisplatin (6% of 78); and for definitive (24%) vs. post-op chemoradiation (9%).

Conclusions: Hearing loss in 22% of HNC patients is clinically significant. The highest proportions in patients had received high-dose cisplatin, definitive chemoradiation, and/or had an OP subsite. The true proportion of hearing loss will be higher, as only 38% had both baseline and follow-up hearing tests, often triggered by symptoms. Baseline and follow-up hearing tests should be routine, and primary preventive hearing loss strategies should be emphasized.

236 The risk of hemorrhage with the use of fluoxetine in the patients aged 60 years and older using KAERS database

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Background: The use of antidepressants has been steadily increasing worldwide. The Selective Serotonin Reuptake Inhibitor (SSRI) has become one of the most broadly used medications in psychiatry. However SSRI is known to have an impact on hemostasis and thus increase the risk of hemorrhages related to serotonin. Fluoxetine is first SSRI drug that is a representative antidepressant drugs. Because older people with clinical depression have high rates of co-morbidities, particularly cerebrovascular disease, they are at high risk of adverse events from most antidepressants. Not a few serious cases of gastrointestinal bleeding and cerebral hemorrhage have been reported, raising concerns about the safety of this drug.

Objective: To investigate risk of hemorrhage by using fluoxetine compared to all other antidepressants in Korean elderly patients from Korea Adverse Event Reporting System (KAERS) database.

Methods: The reports related to antidepressant drugs between December 1988 and December 2016 were identified using the KAERS database. The patients aged 60 years or older with the causality assessments reported higher than possible were included. Total hemorrhage included major bleeding which was divided by gastrointestinal bleeding, and brain hemorrhage. Statistical analysis was used disproportionality analysis. We calculated using the reporting odds ratio (ROR), and their 95% confidence interval (CI).

Results: A total number of 12,005 adverse event reports related to antidepressants (TCA, 28.39%, SSRI, 23.70%, SNRI, 20.03%, Others, 27.88%). The number of reports with fluoxetine related to total hemorrhage, major bleeding, gastrointestinal bleeding, and brain hemorrhage was 5, 4, 1, and 3 respectively. Compared to all other antidepressants, ROR with fluoxetine was 2.51 (95% CI, 1.01-6.21) in total hemorrhage, 5.92 (95% CI, 2.12-16.50) in major bleeding, 2.53 (95% CI, 0.35-18.57) in gastrointestinal bleeding, and 10.31 (95% CI, 3.10-34.26) in brain hemorrhage.

Conclusion: Fluoxetine was associated with total hemorrhage, major bleeding, and brain hemorrhage. The risk of gastrointestinal bleeding was not statistically significant because of low statistical power.

237 Association of Interleukin-4 and Interleukin-10 polymorphisms with Cyclosporine drug-induced hepatotoxicity in Chinese renal transplant recipients

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Objective: To investigate the association between IL-4 and IL-10 gene polymorphisms and susceptibility to liver injury caused by CsA in renal transplant recipients.

Methods: 188 renal transplant recipients were divided into two groups: CsA-induced liver injury group and control group. Two SNP sites of IL-4 gene were identified by multiplex PCR and high-throughput second-generation sequencing (rs2070874, rs2243250). The genotypes of three SNPs (rs1800871, rs1800872, rs1800896) of the IL-10 gene were compared, and the distribution of alleles, genotypes, and haplotypes of the above sites was compared between the liver injury group and the control group.

Results: There was no significant difference in the frequencies of rs2070874 and rs2243250 alleles and genotypes of IL-4 among the 16 liver injury groups and 172 control groups (P>0.05). There was no significant difference in the frequency of IL-10 rs1800871, rs1800872, rs1800896 alleles and genotypes between the two groups (P>0.05). The CAA haplotype of IL-10 was a risk factor for CsA-induced liver injury, which increased the risk of CsA-induced liver injury by 10.68-fold (P=0.013). The remaining haplotypes of IL-10 and IL-4 haplotypes. There was no significant correlation with liver injury caused by CsA (P>0.05). There was a significant difference in the serum concentration of CsA between the IL-4 rs2070874 and rs2243250 loci plus the recessive model at 1 month postoperatively (P Add=0.0023, P Rec=0.0032; P Add=0.0207, P Rec=0.0376.); 3 months after surgery, IL-10 rs1800872 dominant model of CsA plasma concentration has a significant difference (P dom = 0.0479); and at the rest of the post-transplantation, IL-4, IL-10 Gene polymorphism had no significant effect on plasma concentration of CsA (P>0.05).

Conclusion: IL-10 C-A-A haplotype is a risk factor for CsA-induced liver injury; IL-4 and IL-10 polymorphisms have an effect on a small number of CsA serum concentrations.

238 Association of ABCG2 421C>A polymorphisms with adverse reactions caused by mycophenolate mofetil in kidney transplant recipients

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Objective: To investigate the association between the ABCG2 421C> A gene polymorphism and the adverse reactions of mycophenolate mofetil (MMF) in kidney transplant patients.

Methods: Dividing the 236 cases of kidney transplant patients into bone marrow suppression group, gastrointestinal tract reaction group, infection group and control group by adverse reaction type. Statistical analysis on genotype and the age, gender, quality, BMI, dialysis duration, cadaveric kidney or living relative kidney and the oral daily doses and concentration of MMF in 3, 6, 12, 24 and 36 months of the patients was performed using SPSS 20. 0 software. Using HPLC-fluorescence detector to determine the plasma drug concentration of MPA. Using PCR-RFLP to determined single nucleotide polymorphisms genotypes of ABCG2 421C>A, and sending PCR products sequencing directly to verify the accuracy of the agarose gel electrophoresis.

Results: 36 cases of myelosuppression, 15 cases of gastrointestinal reactions , 26 cases were infected and 124 cases had no adverse reaction. The mutation frequency of ABCG2 421C> A gene was 34.32%, wild homozygote was 43.64%, heterozygote was 44.07%, the homozygous was 12.29%. The frequency of AA genotype in gastrointestinal reaction group was significantly higher than that in control group (26.67% vs 9.43%, $\chi 2 = 4.185$, $P = 0.041$) The genotype frequency of ABCG2 421AA genotype was significantly different from that of CC and CA genotype (PCC = 0.002, PCA = 0.036).Logistic regression analysis showed that ABCG2 421AA genotype was an independent risk factor for MMF-induced gastrointestinal reactions after renal transplantation.

Conclusion: ABCG2 421C>A gene polymorphism is associated with adverse reactions caused by MMF after renal transplantation,the individuals carrying ABCG2 421AA are prone to result in MMF-induced gastrointestinal reactions.

239 Fc-γ receptor polymorphisms and overall survival in colorectal cancer patients treated with cetuximab: an assessment of mediation by cetuximab pharmacokinetics

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Aim: Cetuximab inhibits the epidermal growth factor receptor (EGFR) and is used for the treatment of metastatic colorectal cancer (mCRC). The purpose of this study was to investigate whether the effect of polymorphisms in Fc-γ receptor (FCGR) genes FCGR2A (H131R; rs1801274) and FCGR3A (F158V; rs396991) on overall survival (OS) is mediated by cetuximab pharmacokinetics.

Methods: Clinical data was collected as part of the CO.20 phase III, randomized controlled trial of cetuximab (N=375) versus cetuximab+brivanib alaninate (N=376) in EGFR positive, KRAS wild-type mCRC. Genotyping was performed on DNA extracted from whole blood. A marginal Cox proportional hazards model with inverse probability weights was used to estimate direct and indirect effects. PK was modelled as a latent factor and factor scores were used to fit the linear regression mediator model. Genotype was modeled assuming an additive model. Inverse probability weights were calculated based on age, sex, weight, KRAS mutation, serum albumin, platelet count, white blood cell count, performance status, treatment arm, and study site.

Results: No significant mediated effects were observed. The rs1801274 variant was associated with shorter median OS (H/H: 9.6; H/R: 9.0; R/R: 5.6 moths); log-rank p<0.0001); the estimated direct effect (NDE) was hazard ratio (HR): 2.20 (95% confidence interval (CI): 1.20-4.05; p=0.01), the indirect effect (IDE) was HR: 1.00 (95%CI: 0.98-1.03; p=0.81), and the proportion mediated (PM) was 68.9%. The rs396991 variant was associated with longer median OS (F/F: 8.4; F/V: 8.3; V/V: 9.6 months; log-rank p=0.1); the NDE was HR: 0.72 (95%CI: 0.45-1.13; p=0.2), the IDE was HR: 0.99 (95%CI 0.94-1.03; p=0.6) and the PM was 42.4%.

Conclusion: Understanding mediation is useful for identifying modifiable factors between genes and survival outcomes, which may be intervened upon to improve survival. Our results suggest that genetic variation in FCGR2A and FCGR3A influences survival through pathways other than cetuximab pharmacokinetics.

240 The association of FCGR2A and FCGR3A polymorphisms with clinical outcomes in cetuximab-treated patients with metastatic colorectal cancer

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Background: We previously reported that the Fc-gamma-receptor (FCGR) germline polymorphism in the FCGR2A gene (rs1801274; His (H) to Arg (R) substitution) but not FCGR3A (rs396991; Phe (F) to Val (V)) was associated with cetuximab treatment on overall survival (OS) in metastatic colorectal cancer patients (CCTG CO.17 trial). We performed a validation of these results in CO.20, a randomized trial of cetuximab+placebo vs. cetuximab+brivanib for metastatic, chemotherapy refractory, wild type K-RAS colorectal cancer.

Methods: After DNA extraction from whole blood was genotyped, the polymorphism relationships with OS and progression-free survival (PFS) were assessed using log-rank tests and hazard ratios (HR) from Cox proportional hazard models, adjusting for known prognostic factors.

Results: Of 595/725 (82%) K-RAS wild type patients with available DNA and genotyping, those carrying the higher affinity FCGR2A H/H genotype (N=XXX; XX%) had improved OS (HR 0.53; 95%CI:0.XX-0.XX) and PFS (HR 0.65; 95%CI:0.XX-0.XX) compared to those carrying the lower affinity R/R genotype (N=XXX; XX%), corresponding to median absolute benefits of 3.7 months (OS) and 3.3 months (PFS). The H/R genotype (N=XXX) had intermediate outcomes. No significant association was found between FCGR3A genotype and OS or PFS. There was no interaction of FCGR polymorphisms with treatment arm. Patients carrying the double wild type combination of FCGR2A H/H and FCGR3A F/F genotypes (N=45; 7.6%) had significantly better outcomes than other patients, particularly patients carrying the rare (N=11; 2%) R/R+V/V genotype combination, corresponding to median absolute benefits of 12.5 (OS; HR 0.33 95%CI:0.XX-0.XX) and 4.5 (PFS; HR 0.45 95%CI:0.XX-0.XX), months. There were no significant associations between FCGR polymorphisms and either any grade of 3/4 toxicity or skin rash.

Conclusions: In KRAS-wild type, cetuximab-treated patients, the FCGR2A was independently replicated to be associated with clinical outcome without affecting toxicity profiles. Additionally, in this large dataset, FCGR3A appears to modulate the relationship between FCGR2A polymorphism and outcome.

241 Literature review on prevalence of PD-L1 expression among Chinese non-small-cell lung cancer patients

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Objective: To review literatures and summarize the prevalence of Programmed cell Death Ligand 1 (PD-L1) expression among Chinese non-small-cell lung cancers (NSCLC) patients.

Methods: By searching Pubmed website using key words "Carcinoma, Non-Small-Cell Lung" AND "PD-L1" AND "China", tracing citations of searched publications, and excluding studies in cell lines or animal models, reviews and duplicated reports, a comprehensive review was conducted based on information including histological types, tumor stages, antibodies for PD-L1 immunohistochemistry assay, and cut-off values of tumor proportion scores.

Results: From 52 initial searching and their citations, 16 eligible studies covering 2,118 patients were selected and a wide range (25.9% to 86.5%) of PD-L1 expression prevalence was reported. 5 studies (n=847 patients) used samples from adenocarcinoma, 1 (n=156) from squamous carcinoma and 1 (n=66) from lymphoepithelioma-like carcinoma, while 4 (n=625) included multiple histological subtypes and 5 (n=424) did not have information on histological subtypes; antibodies from 7 manufactures, including Proteintech, Sigma-Aldrich, Cell Signaling Technology, Gene-Tech, Abcam, Biolegend and Cell Marque were used for 16 assays; 1 study (n=163) used samples from tumor stage I only and 1 (n=32) from stage III only, while 11 studies (n=1,655) included multiple clinical stages samples and 3 (n=268) did not have such information; 3 (n=213), 10 (n=1,604), 1 (n=42), and 1 (n=139) used 1%, 5%, 12.27%, 50% as cut-off values, respectively, however 1 study (n=120) failed to describe its cut-off value.

Conclusion: Using different antibodies and cut-off values, as well as potential confounding due to samples from varied histological types and clinical stages, huge uncertainties might exist on currently reported prevalence of PD-L1 expression among NSCLC patients in China.

242 Association of two BRM promoter polymorphisms and tobacco exposure with malignant pleural mesothelioma (MPM) risk and survival

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Aim: Brahma (BRM) is a critical ATPase subunit in chromatin remodeling. 6-7bp insertions at two promotor sites (BRM-741/BRM-1321) cause epigenetic suppression of BRM and are reported susceptibility and/or prognostic markers in many cancers. As their epigenetic silencing can be reversed pharmacologically, BRM polymorphisms have therapeutic potential. We evaluated association of these polymorphisms with risk/prognosis of malignant pleural mesothelioma (MPM), with tobacco exposure as an interactive factor.

Methods: MPM and asbestos-exposed controls were recruited in the asbestos-exposure surveillance program. Participants were genotyped for BRM polymorphisms. Multivariable logistic regression assessed risk of MPM in case-control analyses. Association of BRM-variants with overall survival (OS) was assessed by multivariable Cox regression. Secondary subset analyses were stratified by smoking status.

Results: Of 265 MPM cases, 146(55%) were ever-smokers; 51(19%) female; median age 66(range:21-84) years. Median OS and follow-up time were 18 and 15 months, respectively. There were no significant associations of BRM with risk. In contrast, compared to the wild-type, the homozygous-variant of BRM-741 and BRM-1321 were associated with lower OS, with adjusted hazard ratio (aHR)=2.56[95%CI:1.7-3.8] and 2.07[95%CI:1.4-3.1], respectively. Compared to patients carrying the double wild-type, patients with double-homozygous had lower OS (aHR=2.70[95%CI:1.7-4.4]). There were significant differential effects of BRM polymorphisms on MPM risk by smoking status: among ever-smokers, BRM homozygous-variants in BRM-741, BRM-1321, or both lowered risks (adjusted OR(aORs):0.18-0.28), while never-smokers had increased risk by carrying the homozygous variants (aORs:2.7-4.4). Likewise, a similar differential effect by smoking status was seen in prognosis: there was no association between BRM polymorphisms and OS in ever smokers, but in never-smokers, the aHR of carrying homozygous-variants of BRM-741, BRM-1321 or both were 7.7[95%CI:3.8-16], 4.0[95%CI:2.1-7.7], and 8.6[95%CI:3.7-20], respectively.

Conclusion: Never-smokers who develop MPM have an increased chance of carrying BRM homozygous variants, which results in worse prognosis. In contrast, in ever-smokers, there may be a protective effect, with no difference in overall survival.

243 The effect of WFS1 and ABCC2 heritable variants on cisplatin-induced ototoxicity in head and neck squamous cell carcinoma (HNSCC) patients

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Objective: Ototoxicity is a common adverse drug reaction associated with cisplatin therapy and with radiation to the HN region. We evaluated the differential effect on hearing impairment in HNSCC patients by candidate polymorphisms of genes associated with either hearing loss or cisplatin function.

Methods: In this observational study of locally-advanced HNSCC patients treated with cisplatin chemoradiation, hearing impairment attributed to treatment was defined as ≥grade 2 audiometric change from baseline to post-treatment, evaluated within 18 months of completing therapy (CTCAE v4.02). Patients were genotyped for 30 polymorphisms using Sequenom. Logistic regression evaluated associations between genetic variants and ototoxicity. Cox regression assessed relationships between genetic variants and locoregional control (LRC), distant control (DC), disease free survival (DFS) and overall survival (OS).

Results: Of 246 patients who had audiometric testing pre- and post-chemoradiation, 79% were male; 76%, oropharyngeal cancers; 11%, oral cavity cancers; 8%, laryngeal cancer; 91%, stage IV; 58% had hearing loss. Two polymorphisms had significant associations with hearing loss post treatment: WFS1 rs62283056 and ABCC2 rs3740066. In an additive inheritance model, individuals with WFS1 variants had a significantly decreased risk of ototoxicity (P = 0.012; adjusted odds ratio (aOR) = 0.56; 95% CI, 0.4-0.9, per increase in one minor allele), while the minor allele of ABCC2 was associated with greater risk of ototoxicity (P = 0.016; aOR = 1.68; 95% CI, 1.1-2.6). In contrast, the same genetic variants were not associated with LRC, DC, DFS or OS in a larger cohort of 642 HNSCC patients.

Conclusions: WFS1 genetic variant is associated with differential hearing loss in LA-HNSCC patients. An ABCC2 variant, involved with removal of cisplatin from cells, is associated with increased cisplatin-induced ototoxicity. The same genetic variants were not associated with any efficacy outcomes. This information could be useful in the development of predictive models for cisplatin-induced ototoxicity.

244 Two BRM promoter polymorphisms do not predict susceptibility or prognosis of thymoma

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Aim/Objective: Brahma (BRM) is a critical protein subunit in chromatin remodeling, and insertions/deletions at its two polymorphic promotor sites (BRM-741 and BRM-1321) have been reported as susceptibility and/or prognostic markers in many malignancies. As epigenetic silencing of BRM can be pharmacologically reversed, BRM polymorphisms may have therapeutic implications. We evaluated whether BRM-741 and BRM-1321 polymorphisms influence overall risk, survival, and time-to-progression of thymoma.

Method: Thymoma cases and matched healthy controls were recruited in a comprehensive cancer centre. Study participants' peripheral blood samples were genotyped for BRM promoter polymorphisms. Multivariable logistic regression assessed risk of thymoma in case-control analyses. Association of BRM variants with overall survival (OS) and time-to-progression or recurrence (TTP) was assessed by multivariable Cox regression.

Result: Of 237 cases of histologically diagnosed thymoma and 948 age-, gender-matched healthy controls, thymoma patients had median age of 53(range:17-84) years; 121(51%) were male; 76(32%) had a history of myasthenia gravis. Median follow-up time was 7 years. 79% of patients were recurrence-, progression-free at 10-year-follow-up (95% CI: 74-86%), and 81% of patients were alive at 10-year-post-diagnosis (95%CI:75-87%). Frequency of homozygous variants for either gene was not significantly different between thymoma cases and controls: homozygous BRM-741(OR=1.0; 95%CI:0.6-1.8; P=0.95), homozygous BRM-1321(OR=0.59; 95%CI:0.3-1.0; P=0.07) or double homozygous variants in both loci(OR=0.69; 95%CI:0.3-1.4; P=0.29). No association between BRM-741/BRM-1321 and OS and TTP was detected (For homozygous BRM-741, OS P=0.74, TTP P=0.93; for homozygous BRM-1321, OS P=0.39, TTP P=0.93). Consistently, there was also no association between double homozygous variants and OS and TTP (Double homozygous, OS P=0.64, TTP P=0.48). Heterozygous variants were also not associated with either risk or outcome.

Conclusion: Results of this study do not support use of BRM promoter polymorphisms as susceptibility or prognostic markers for thymoma. Molecular biologic mechanisms of risk and prognosis remain elusive in malignant thymoma.

245 The antiphospholipid antibody syndrome and risk of newonset thrombosis: a cohort study using laege claim database in Japan

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Background: Studies using data from Western countries have raised concerns that treating pregnant women with antiphospholipid antibody syndrome may increase the risk of some thrombosis disease in their later life. However, to date, the studies are not conclusive. We therefore examined the association using claims data collected in Japan.

Methods: This retrospective cohort study was based on claims data of the women from January 2005 to July 2014, obtained from the Japan Medical Data Center. Information on antiphospholipid antibody syndrome and onset of thrombosis was diagnosed by ICD-10 code from the database. We used Cox regression analysis to evaluate the incidence of thrombosis between women with and without antiphospholipid antibody syndrome.

Results: Of about 170 thousand women, 1500 women was diagnosed as antiphospholipid antibody syndrome. Multivariable Cox regression analysis showed that the prevalence of antiphospholipid antibody syndrome during the pregnancy was significantly higher with the incidence of stroke than with non-use (hazard ratio [OR], 1.6; 95% confidence interval [CI], 1.1, 1.8).

Conclusions: In this study, we found the significant association between APS during pregnancy and thrombotic diseases in Japan. Further studies are necessary before an association can be concluded.

246 Cefoperazone/Sulbactam-associated coagulopathy and bleeding

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Background: To describe the effect of Cefoperazone/Sulbactam on the blood coagulation function, to investigate the incidence of coagulopathy and bleeding in patients receiving Cefoperazone/Sulbactam and to identify its rescue strategies.

Methods: PubMed databases were searched through October 10, 2017. Clinical trials and case reports were eligible. Data on the incidence, mechanisms, risk factors, location, timing, minimization strategies and treatment of Cefoperazone/Sulbactam associated coagulopathy and bleeding were extracted and analyzed.

Results: Thirty-two studies were included. Of these, nineteen were clinical trials and 13 were case reports. The frequency of prolonged prothrombin time and bleeding with cefoperazone or cefoperazone/sulbactam ranged from 0 to 64.2% and 0 to 49.2% respectively. NMTT（N-methyltetrazole）side chain plays an important role in this process but the effects of Cefoperazone on intestinal bacteria, prostaglandin, platelet and the purity of products also should be considered. Risk factors include liver disease, renal dysfunction, malnutrition, advanced age, and so on. The most common bleeding cases were hematemesis. Prophylactic administration of vitamin K is recommended for patients with risk factor.

Conclusion: Clinical staff should realize Cefoperazone/Sulbactam-associated coagulopathy and bleeding and fully understand possible mechanisms. Care must be taken to patients with high-risk factors. Once coagulopathy or bleeding appears, vitamin K should be given. If necessary, fresh plasma infusion should be performed. Still, more studies are required to fully know and cope with such adverse effect.

248 Analysis of the efficacy and safety of remifentanil and fentanyl in abortion: a systematic review and meta-analysis

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Objective: To systematically review the efficacy and safety of remifentanil and fentanyl in abortion, in order to generate evidence of the value of the medicines.

Methods: The randomized controlled trials of remifentanil versus Fentanyl in abortion were systematically searched in the Cochrane Library、MEDLINE、EMBASE、CNKI、VIP and WanFang data, to identify the primary full Chinese and English literatures with the experimental group of remifentanil and the controlled group of fentanyl (combined with the same anaesthetic) and published between January 2007 and March September 2017. Two reviewers independently screened literatures, extracted data and assessed risk of bias of individual trials, and the overall quality of evidence. Then, meta-analysis was performed using RevMan 5.1 software.

Results: 15 trials with 2180 patients most at low risk of bias were identified. The results of meta-analysis showed that: ①Hemodynamic changes: There were no significant differences between Remifentanil group and Fentanyl group for SBP， DBP and MAP changes at prepoperative, intraoperative and postoperative, but the changes were more stable in Remifentanil group. ② Emergence time: Compared with Fentanyl group, emergence time (WMD = -2.97, 95％CI -4.84 to -1.10, P=0.002) were significantly shorter in Remifentanil group． ③Adverse reactions: Compared with Fentanyl group, the incidence rate of intraoperative body movement (RR = 0.42, 95％CI 0.21 to 0.83, P=0.01) were significantly lower in Remifentanil group. There were no significant differences between Remifentanil group and Fentanyl group for the incidence rates of respiratory depression, nausea and vomit.

Conclusion: As an ultra-short opioid receptor anesthesia, comparing with fentanyl, remifentanil has more stable performance on hemodynamic changes and the advantages of emergence time, as well as less risk of intraoperative body movement.

249 The effect of fixed combination of valsartan-amlodipine on the primary hypertension: a systematic review and meta-analysis

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Objective: To evaluate the effect of fixed combination of valsartan-amlodipine on the primary hypertension for providing reference for the rational drug use.

Method: Comprehensive searches were performed of Web of Science, Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure, WanFang database, and VIP database by the key words of hypertension, fixed-dose combination, fixed combination, valsartan, and amlodipine from 1997 to 2017. Trials of fixed combination of valsartan-amlodipine selection, data extraction, quality assessment were conducted according to the Cochrane review standards, and data analyses were conducted using RevMan 5.3 software.

Results: 25 trials with 23761 patients about effect of fixed combination of valsartan-amlodipine on the primary hypertension were finally included. The effect of fixed combination of valsartan-amlodipine was better than that of the control group [90.62% vs 75.58%, pooled OR=2.98, 95%CI（2.02～4.40）, P<0.001], while the incidence of adverse drug reactions was higher than that of the control group [17.58% vs 16.50%, pooled OR=0.66, 95%CI（0.50～0.87）, P=0.003].

Conclusions: The fixed combination of valsartan-amlodipine is more effective for the primary hypertension. It is necessary to strengthen the medication education of valsartan-amlodipine in clinical application. The data provides the evidence for drug rational use and drug policy development.

250 Limited knowledge of chronic kidney disease among high-risk diabetic and hypertensive patients in India: Evidence from a cross-sectional study

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Objective: Diabetic Kidney Disease (DKD) is considered a major public health problem for both the patient and the healthcare system. Diabetes and hypertension are the two major cause of developing Chronic Kidney Disease (CKD) and also the most common cause of end-stage renal failure. Epidemiological studies found poor knowledge of CKD among the general public. So, this study is aimed to assess the CKD awareness among high-risk diabetic and hypertensive patients.

Methods: This was a cross-sectional study conducted over a period of one year. The study protocol was approved by Jamia Hamdard Institutional Ethics Committee. Patients with confirmed type 2 diabetes mellitus were included in the study. Patients were excluded from the study if they were receiving dialysis or had a history of a kidney transplant. A validated questionnaire was used to assess the CKD awareness. The continuous variable descriptive statistics and trends in groups were calculated using chi-square test. Statistical analysis was performed using SPSS v22.

Results: A total of 315 patients completed the study. The mean age of the patient was 53.97±10.62 years. Only 34% of patients correctly identified diabetes and hypertension as the risk factor for CKD, while 48% were aware of the function of kidney in the human body. Less than 1 in 10 patients were aware that kidney transplant is the best medical treatment for end-stage renal failure patients. Kidney disease knowledge was significantly lower among older patients (>50years of age) {p= 0.029}. Statistically significant association was observed between kidney disease knowledge and education status (p = 0.000), employment status (p= 0.000), and income status (p= 0.000). No association was observed between kidney disease knowledge and hypertension stage, CKD stage, duration of diabetes and co-morbidities.

Conclusion: We found poor knowledge of kidney disease among high-risk diabetic and hypertensive Indian patients. The government should start a CKD awareness programme to deal with this devastating co-morbid condition.

251 Association between hemoglobinA1c levels and ischemic stroke events: a systematic review and meta-analysis

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Aim: A number of studies have reported a strong association between increased HbA1c levels and high risk for ischemic stroke events. However, the role of HbA1c in the prediction of ischemic stroke is still unclear. The systematic and meta-analysis was conducted to address the association between HbA1c levels and ischemic stroke events as well as other outcomes including hemorrhagic stroke, all strokes, coronary heart disease, cardiovascular disease and all-cause death.

Methods: We searched seven major electronic databases; EMBASE, Scopus, PubMed, Cochrane Library, Google Scholar, Thai Index Medicus and Thai Medical Index without language restriction from the inception to 18 October 2017. The studies investigating the relationship between HbA1c levels and ischemic stroke were included in the meta-analysis. Subgroup analysis for continents, diabetes mellitus status, clear and unclear HbA1c measurements, as well as dose-response relationship between HbA1c levels and ischemic stroke were also performed to examine the influence of different variables to ischemic stroke events.

Results: A total of eight studies comprising of 168,256 participants were included for analysis. In the meta-analysis, the association between HbA1c levels > 6.5 was significantly associated with an increased risk of ischemic stroke [HR 1.58, 95% CI, 1.30-1.87], all strokes [HR 1.70, 95% CI, 1.51-1.90], cardiovascular disease [HR 1.73, 95% CI, 1.43-2.02], coronary heart disease [HR 2.21, 95% CI, 1.68–2.74] and all-cause death [HR 1.70, 95% CI, 1.32-2.07], and trend to increase risk of hemorrhagic stroke [HR 1.26, 95% CI, 0.89-1.64]. Similarly, the risk of ischemic stroke also increased dramatically when HbA1c levels increased to 6.5 according to the dose-response relationship. The results on ischemic stroke outcome remained identical after subgroup analysis according to HbA1c levels.

Conclusions: HbA1c levels higher than 6.5 is significantly associated with the increased risk of ischemic stroke, all strokes, cardiovascular diseases, coronary heart diseases and all-cause death.

252 Impact of incretin-based therapies on arthralgia among type 2 diabetes: a systematic review and network meta-analysis

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Aim: Incretin-based therapies, including Dipeptidyl peptidase-4 inhibitors (DPP-4i) and Glucagon-like peptide-1 receptor agonists(GLP-1RAs), have led to concerns about its safety such as arthralgia in patients with type 2 diabetes(T2DM). To systematically review the effects of DPP-4i and GLP-1RAs on arthralgia among T2DM.

Methods: Medline, Embase, Clinical trials and Cochrane library were searched from inception through 2017 to indentify randomized clinical trials(RCTs) assessed safety of incretin-based therapies in T2DM.

Results: 215 RCTs (92471 participants) were enrolled in this study, including 21 treatments: 9 DPP-4i(Alogliptin, Anagliptin, Gemigliptin, Linagliptin, Saxagliptin, Sitagliptin, Teneligliptin, Trelagliptin, Vildagliptin), 6 GLP-1RAs(Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Taspoglutide), placebo and 5 traditional anti-diabetic drugs(Insulin, Metformin, Sodium-dependent Glucose co-Transparents-2(SGLT-2), Sulfonylureas(SUs), and thiazolidinediones(TZDs)). Significant decreased risk on arthralgia were found when Taspoglutide and Dulaglutide versus Insulin, Placebo, SUs(range of ORs: 0.37-0.60). Compared with Metformin, Vildagliptin, Saxagliptin and Linagliptin significantly increased the incidence of arthralgia, with OR of 2.81(95%CI: 1.29-6.12), 3.06(95%CI: 1.36-6.86) and 3.13(95%CI: 1.28-7.69), respectively. Ranking probability analysis was performed later, which indicated Taspoglutide, Metformin and Dulaglutide decreased risk of arthralgia most with probabilities of 93.1%, 89.6%, 83.5% while Linagliptin, Saxagliptin and Trelagliptin showed a poor performance with the lowest probabilities of 14.3%, 19.0%, 21.9%.

Conclusion: Taspoglutide and Dulaglutide seem to show a protective effect in T2DM on arthralgia. However, Linagliptin, Saxagliptin and Trelagliptin is associated with increased risk on arthralgia.

253 The hypoglycemia safety of dipeptidyl peptidase-4 inhibitors among patients with type 2 diabetes mellitus: A systematic review and network meta-analysis

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Aim: To systemically evaluate the dipeptidyl peptidase-4 inhibitors (DPP-4is) on hypoglycemia safety in type 2 diabetes mellitus (T2DM) patients.

Methods: The Cochrane Library, Embase, Medline and Clinicaltial.gov were searched from inception through September 30th, 2017 and randomized controlled trials (RCT) comparing DPP-4is with other treatments in T2DM patients were identified. Trials with access data on hypoglycemia were included. Random-effects pairwise and network meta-analysis were used to estimate the relative effect of hypoglycemia as odds ratios (ORs) and their 95% confidence intervals (CIs). As important assumptions in NMA, the heterogeneity, consistency and publication bias were explored by the predictive interval plot, node-splitting method and funnel plot respectively. The trial quality and treatment ranks were assessed according to GRADE tool and the surface under the cumulative ranking curve (SUCRA).

Results: 147 trials enrolling 91886 patients and 13 treatments (alogliptin, linagliptin, sitagliptin, saxagliptin, vildagliptin, placebo, GLP-1RAs, insulin, metformin, SGLT-2, sulfonylureas, thiazolinedione and □-glucosidase inhibitors) were included in final analysis. In NMA, increasing risk were found when vildagliptin (OR, 1.41; 95%CI: 1.02, 1.96), sitagliptin (OR, 1.37; 95%CI: 1.08, 1.79) and linagliptin (OR, 1.69; 95%CI: 1.18, 2.44) versus placebo. The significant risk of SUs was also observed when compared with other treatments. Similar improved hypoglycemia safety was also seen in the comparisons between vildagliptin (OR,0.42; 95%CI: 0.19, 0.93), sitagliptin (OR, 0.41; 95%CI: 0.18, 0.93), saxagliptin (OR, 0.30; 95%CI: 0.12, 0.76), alogliptin (OR, 0.28; 95%CI: 0.10, 0.78) and insulin. TZD, alogliptin and placebo were estimated to have the best hypoglycemia safety with SUCRA 85.3%, 77.0% and 76.6% respectively.

Conclusion: DPP-4is are good at hypoglycemia safety overall in which alogliptin performed best.

254 Comparative efficacy and safety of hydromorphone and morphine in post-cesarean section analgesia: a systematic review and meta-analysis

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Objective: To systematically compare the efficacy and safety of hydromorphone and morphine in post-cesarean section analgesia.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Embase, CNKI, WanFang Data, VIP, Sinomed databases were electronically searched to identify randomized controlled trials (RCTs) of hydromorphone vs. morphine in the treatment of postoperative analgesia after cesarean section up to December 2017. Two reviewers independently screened literatures, extracted data and assessed risk of bias of individual trials, and the overall quality of evidence. The primary outcomes were VAS and Ramsay scores and the incidence of adverse reactions. Sub-group analysis were performed for trials with different administration approaches. Random-effects inverse variance model was used to perform the meta-analysis with RevMan 5.3.

Results: 7 trials with 586 patients most at low risk of bias were identified, which reported the VAS and Ramsay scores at various time and the incidence of adverse drug reactions. The postoperative VAS score of the hydromorphone group with epidural anesthesia pump (PECA) at 6,12,24 and 48 hour were 0.23[WMD,95%CI:-0.38,-0.08,P=0.003,I^2=0%], 0.56[WMD,95%CI:-1.10,-0.02,P=0.04,I^2=0%], 0.48[WMD,95%CI:-0.76,-0.20,P=0.0008, I^2=0%] and 0.41[WMD,95%CI:-0.74,-0.08,P=0.01, I^2=0%] lower than the morphine group. There were no statistically significant difference between their postoperative Ramsay scores. The incidence of skin pruritus of the hydromorphone group with PECA, epidural infusion and combined administration were 43%[RR,95%CI:0.22,0.85,P=0.01,I^2=0%], 2%[RR,95%CI:0.00,0.38,P=0.008,I^2=0%] and 3%[RR,95%CI:0.00,0.46,P=0.01,I^2=0] of the morphine group. The incidence rate of vomit of the hydromorphone group with combined administration was 6%[RR,95%CI:0.00,1.00,P=0.05,I^2=0%].There were no statistically significant difference of the incidence rates of nausea and somnolence.

Conclusion:The current evidence demonstrate that, compared with morphine, hydromorphone has better postoperative analgesia performance and less risk of getting skin pruritus and vomit after cesarean section. Considering that the overall quality of evidence was low for the primary outcomes, and the relatively small pooled sample size, more well-conducted, adequately powered randomized controlled trials are necessary to further verify the above conclusion.

255 Biomedical and therapeutic predictors of survival time and mortality of adult HIV/TB co-infections; a retrospective cohort study

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Objectives: Comprehensive assessment of biomedical and therapeutic predictors of survival time (ST) and mortality of TB/HIV co-infected patients.

Methods: A retrospective cohort study design was used to review data of 364 confirmed TB/HIV patients from standard ART and TB registry of Ministry of Defense Teaching Hospital, Ethiopia, treated between 2014 –2016. Patient mean age was 36.7 years. All-cause mortality was excluded but HIV/TB co-infection. For the survival analysis, the outcome of interest was 'treatment failure' or 'death'. A univariate descriptive statistical analysis was performed using a non- parametric procedure, Kaplan -Meier (KM) method to estimate overall survival (OS) time, while Cox proportional hazard model was used in multivariate Cox regression analysis to determine a possible association of predictor variables and to obtain adjusted hazard ratios. P-value was set at, 0.05, log likelihood ratio test at 0.10. Data were analyzed using SPSS version 18.0.

Results: There was no significant difference in the survival curves of male and female patients (Log rank statistic =0.005, d f=1, p=0.945) and among different age group (Log rank statistic =28.622, d f=40, p=0.910). The mean overall survival (OS) time was 24.8 months (95%CI: 18–31). The mean ST for women was 29.8 months (95%CI: 76.6–694) while for men was 17.9 months (95%CI: 13.5–22.2). Survival time varies by CD4 cell count, WHO clinical stage; functional status, TB Rx regimen, TB Rx Phase and type of HAART and multivariate Cox regression showed that these factors were also important predictors of mortality.

Conclusions: Biomedical and therapeutic monitoring of HIV/TB co-infected patients with low CD4 cell count, advanced WHO stages III & IV, ambulatory and bedridden functional status, diagnosed TB site, TB treatment Phase and HAART regimen is necessary to improve survival and reduce the risk of death of patients at initiation, during anti-TB treatment and ART follow up period.

256 The association between HPV and prognosis of unknown primary carcinoma in head and neck region: a systematic review and meta-analysis

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Aim: As it has been postulated that the majority of cancer of unknown primary in head and neck region (CUPHN) likely originate from the oropharynx, where human papillomavirus (HPV) is a known risk and prognostic factor. We aimed to compare the prevalence and outcome prognosis of HPV-positive CUPHN patients with HPV-negative CUPHN patients.

Methods: Medline, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library and Web of Science were searched in this study, without Languages restriction. Studies were limited to observational studies and clinical trials that reported on the survival rates of patients with CUPHN which presented as HPV positive vs. HPV negative. Additionally, matched oropharyngeal cancer (OPC) studies from the same institution of each included CUPHN study were searched to compare the HPV prevalence in CUPHN and OPC.

Results: Seventeen studies with overall survival (OS) and progression-free survival (PFS) data were included in this study, and seventeen institution-matched OPC studies were presented in the comparison of HPV prevalence. The pooled results showed that CUPHN patients with HPV positive status presented to have a favorable OS and PFS prognosis when compared to those HPV negative patients. The HPV prevalence rates between CUPHN and OPC patients (institution-matched) were quite similar, with difference to be only 12% ($p<0.00001$).

Conclusions: Our results suggest that CUPHN tend to have a similar HPV-related prevalence and prognosis with OPC, indicating that HPV may be a favorable maker to predict outcomes for CUPHN patients, or even provide clues to detect their potential primaries to help guiding treatments.

257 Efficacy and safety of biosimilar drugs compared to reference biologics in oncology: systematic review and meta-analysis of RCTs and NRCTs

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Objective: With a number of topselling biologics used in facing patent expiration, biosimilar products for therapeutics for cancer therapy and the supportive management of treatment-related side effects have been developed. The aim of this meta-analysis was to evaluate the clinical efficacy and safety of biosimilar drugs in oncology.

Methods: PubMed, Embase, the Cochrane library, ClinicalTrials.gov, ISI Web of Science, the Chinese databases were searched from inception to the end of 21 Dec 2017, supplemented by a scanning of oncology conference sites and reference lists of relevant systematic reviews. The outcomes of mAb biosimilars include: efficacy outcomes (e.g., overall response rate) and safety outcomes (e.g., neutropenia rate); the outcomes of epoetin biosimilars include: efficacy outcomes (e.g., mean of increasing hemoglobin) and safety outcomes (e.g., thromboembolism rate); the outcomes of G-CSF biosimilars include: efficacy outcomes (e.g., duration of severe neutropenia) and safety outcomes (e.g., bone pain rate). Binary outcomes were pooled by using risk ratio (RR) with 95% CIs and continuous outcomes were combined by using mean differences (MD) with 95% CIs. Subgroup analysis and sensitivity analysis were also conducted, GRADE approach was used to rate the quality of evidence.

Results: 41 comparative studies were included: 6, 4 and 8 RCTs are eligible for Rituximab biosimilars, Bevacizumab biosimilars and Trastuzumab biosimilars respectively; 5 cohort studies and 1 RCT are for epoetin alfa biosimilars; the rest 11 RCTs and 6 cohort studies belong to G-CSF biosimilars. Overall difference in efficacy outcomes and safety outcomes between reference and biosimilars was not statistically significant, low or moderate quality of evidence. Subgroup analyses did not suggest the difference in the effects of biosimilars between different types of tumors and types of biosimilar drugs. This observation was robust through most of the sensitivity analyses.

Conclusion: The current available evidence demonstrated the similar efficacy and safety profile of biosimilars compared to reference biologics in oncology.

258 Epidemiological characteristics of hospitalized patients with complicated intra-abdominal infection: a cross-sectional analysis using electronic medical records

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Aim: Complicated intra-abdominal infection (cIAI) encompasses a wide variety of serious infections ranging from appendiceal abscesses to more severe conditions. cIAI is an important cause of morbidity and is frequently associated with a poor prognosis. The prevalence and distribution of cIAI among different hospital departments is not well described in the published literature.

Methods: This analysis was conducted using the West China hospital EMR database. All patients with a cIAI diagnosis were identified from 2012-2014. A cIAI diagnosis was defined as an elevated white blood cell count (WBC > 9.5*109/L) and the presence of an ICD-10 code for cholecystitis, appendicitis, or peritonitis. In addition, physician notes were examined to identify patients with a discharge diagnosis indicative of an intra-abdominal infection. Identified cIAI patients were further evaluated for inclusion based on physical examination and lab results. The annual prevalence of cIAI and all-cause mortality were calculated and stratified by hospital department and infection type.

Results: There were approximately 500,000 inpatients discharged from West China hospital during the study period. The annual prevalence of cIAI was 0.3%. The majority of cIAI patients were discharged from the surgical department (58.9%), followed by internal medicine (34.5%) and ICU (6.6%). Within the surgical department, the top 3 sub-departments were the gastrointestinal department (35.8%), hepatobiliary and pancreatic department (25.7%), and the biliary department (22.7%). The overall in-hospital mortality rate was 5.2% among all cIAI inpatients. The highest mortality rates were identified in the ICU (28.8%) and the internal medicine department (9.2%). The majority of cIAI cases were appendicitis (30.9%), followed by peritonitis (22.6%) and cholecystitis (20%). Mortality was highest among cIAI patients with peritonitis (12.1%). The top 5 identified comorbidities were hypertension (17.0%), liver disease (16.92%), cancer (13.2%), diabetes (10.2%) and renal failure (7.0%).

Conclusion: Overall, cIAI cases were more likely to occur in the surgical department and all-cause mortality was highest in the ICU setting.

259 A database study to estimate the background incidence of intussusception in Liujiang County, China

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Objective: In 2015, a clinical trial was conducted to evaluate the safety and efficacy of RotaTeq (MSD rotavirus vaccine) among children in 5 sites (including Liujiang County) in the City of Liuzhou, China. Estimating pre-vaccine incidence rate of Intestinal intussusception (IS) would provide context for rates observed after vaccine introduction; however, data on IS incidence in China are limited. We conducted a feasibility assessment to estimate the background rate of IS in children under 1 year of age in Liujiang County.

Methods: This was a retrospective feasibility assessment using the electronic medical record (EMR) of 4 local hospitals to identify potential IS cases in the same area where the clinical trials were conducted. Potential IS cases occurring in the study hospitals between 01-January-2014 and 31-December-2015 were identified by searching the EMR for the keyword "intussusception" and certain demographic criteria (e.g., age <1 year, residence in Liujiang). The medical records of potential cases were reviewed by physicians to confirm the diagnosis of IS. The total infant population in the Luijian County was used as a denominator to estimate IS incidence rates.

Results: A total of 24 confirmed IS cases were identified in the target population, most of them in infants 5-11 months of age. Among them, 7 IS cases were in infants who later received rotavirus vaccine and 17 cases were infants who did not receive any rotavirus vaccine in the 1st year of life. We estimated that the background rate of IS in Liujiang County could range from 138 (95% CI: 81, 221) to 172 (95% CI: 111, 257) per 100,000.

Conclusions: This feasibility assessment provided background incidence rates of IS in a small area of China. The assessment was retrospective and conducted in only 4 local hospitals, so may have missed cases. Nevertheless, the rates found were in line with rates reported from China and other neighboring Asian countries.

260 The methodological research on dose-effect adjustment in network meta-analysis: a simulation and application study

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Objective: To explore the potential influence and solution of dose-related methodological issues in network meta-analysis.

Methods: In the simulation study, a group of 24 dose-related NMA data including low, medium and high doses were generated. Lumping, splitting and dose-response NMA models which were based on Bayesian vague priors and dose-adjustment priors respectively were built and applied to the data to calculate the effect estimation and model fit using the Bayesian Markov Chain Monte Carlo methods. In the application study, the RCTs based on type 2 diabetes patients of DPP-4 inhibitors were searched to build the dose-related network evidence of hypoglycaemia safety which was used to verify the previous result.

Results: In the simulation study, the incidence set and node selection might be the potential influence factor in estimating the ORs while dose-response relationship had little impact on it. The estimations in efficacy situations were robust in which dose-level models fitted the data better but the estimations in safety situations varied widely with a wide confidence interval sometimes in which no fit differences were found among models. The similar results between SNMA and DRNMA models showed that the dose-response relationship had little influence in NMA. In application study, a total of 15873 articles were searched and 147 RCTs enrolling 13 anti-diabettic drugs were included. The results were consistent with simulation conclusion. Compared to controls, the hypoglycaemia results of DPP-4 inhibitors were consistent with previous studies.

Conclusion: Both simulation and application study showed that dose-response relationship had little impact in NMA. It was not necessary to adjust the dose-response relationship by DRNMA model. LNMA and SNMA models based on vague priors were able to handle the analysis. The verification results of DPP-4 inhibitors were consistent with simulation study, compared to controls, the hypoglycaemia results of DPP-4 inhibitors were consistent with previous studies.

261 Impact of gene polymorphisms involved in folate metabolism on methotrexate toxicity in osteosarcoma: a systematic review and meta-analysis

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Objective The associations between methotrexate toxicity and methylenetetrahydrofolate reductase (MTHFR), reduced folate carrier (RFC1), multiple drug resistance gene (MDR1/ABCB1) polymorphisms in osteosarcoma have been widely investigated, but the conclusions remained inconsistent. Therefore, the systematic review was conducted to draw a more precise conclusion of the association.

Methods Databases including MEDLINE, EMBASE, Clinical Trials.gov, China National Knowledge Infrastructure (CNKI), WANFANG, and Chinese Biomedical Database (CBM) were searched from inceptions to March 2018. The references of studies included were manually searched. Newcastle-Ottawa scale (NOS) was adopted to assess quality.

Results Totally eight studies with high quality were included (average score of 8 points), with 6 and 5 studies investigating MTHFR C677T and A1298C respectively, 4 studies on RFC1 G80A and 2 studies on ABCB1 C3435T. The meta-analyses indicated MTHFR C677T was associated significantly with renal toxicity (TT vs. CT/CC: OR=7.39, 95% CI=3.26-16.73), severe renal toxicity (TT/CT vs. CC: OR=12.35, 95% CI=3.28-46.42), mucositis (TT vs. CT/CC: OR=2.18, 95% CI=1.21-3.91) and severe mucositis (T vs. C: OR=2.04, 95% CI=1.06-3.03). The qualitative analyses suggested MTHFR A1298C might be associated with lower risk of severe toxicity, such as severe hepatotoxicity (AA/AC vs. CC: OR=0.52, 95% CI=0.13-2.17) . RFC1 G80A was found to be associated with mild mucositis (AA/AC vs. CC: OR=16.80, 95% CI=1.44-195.68) and severe mucositis (AA/AC vs. CC: OR=0.06, 95% CI=0.01-0.69). ABCB1 C3435T was found to be associated with mucositis (CC vs. TT: OR=7.5, 95% CI=1.3-44).

Conclusion To our knowledge, it's the first systematic review to investigate the associations in patients with osteosarcoma. Overall, based on evidences with good quality but limited data, MTHFR C677T plays a greater role in increasing methotrexate toxicity while MTHFR A1298C tends to lower the risk of severe toxicity. RFC1 G80A and ABCB1 C3435T may play a minor role in mucositis. However, well-designed and large-scale studies in osteosarcoma are still required to verify the conclusions and promote personalized medicine better.

262 Effects of combined medication on the safety of high-dose methotrexate: a systematic review

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Abstract: Objective To evaluate the safety of high-dose methotrexate (HD-MTX) when co-administrated with other medication.

Methods: Databases including MEDLINE, EMBASE, Clinical Trials.gov, China National Knowledge Infrastructure (CNKI), WANFANG Data, and Chinese Science and Technology Journal Database (CBM) were searched from inceptions to March 2018. The references of studies included were manually searched. Two reviewers independently screened records to identify eligible studies, extracted data and assessed their qualities.

Results: Totally eight studies with general quality were included. Combining with non-steroidal anti-inflammatory drugs (NSAIDs) led to higher plasma concentration of MTX and higher risk of acute kidney injury (21.4% vs. control group 8.9%). Combining with proton pump inhibitors (PPI) resulted in delayed excretion of MTX. Combining with penicillin decreased the clearance of MTX (about 3-19 days down to normal vs. control group 2-12 days). Combining with mercaptopurine (6-MP) could increase the risk of mucosal toxicity and myelosuppression. Combining with cisplatin increased the level of total protein as well as other markers of renal damage.

Conclusion: The review integrates available evidence to provide reference for combined medication. When co-administrated with some drugs (such as NSAIDs, PPI, penicillin, 6-MP, cisplatin or others), MTX's pharmacokinetics may change and then severe adverse events occur by displacing plasma protein or blocking MTX's renal secretion or inhibiting MTX's clearance or lowering the urine pH. Therefore, in order to lower the risk of drug interactions and insure patients' safety, combined medication should be evaluated fully before administrating HD-MTX and plasma concentration should be monitored more closely. Timely measures should be taken when indispensable.

263 The comparative nephrotoxicity potential of colistin and polymyxin B: a meta-analysis

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Objective: The relative nephrotoxicity of colistin and polymyxin B remains uncertainty, thus we aimed to perform a meta-analysis of head-to-head studies to systematically evaluate the comparative nephrotoxicity of colistin and polymyxin B.

Methods: A meta-analysis was carried out by searching PubMed, Embase, the Cochrane Database, and ClinicalTrials.gov from inception to Mar 30, 2018. We included head-to-head studies comparing colistin and polymyxin B; studies that reported risk estimates [relative risk (RR), odds ratio (OR) or hazard ratio (HR)] with 95% confidence intervals (CIs) for events of nephrotoxicity associated polymyxin use. A RR value with 95% confidence interval (CI) was used to calculate the pooled estimates with random-effects models.

Results: Six cohort studies and one case-control study were included. A total of 1616 patients treated by polymyxins and 649 cases of nephrotoxicity were included. Compared with polymyxin B, the RR (95% CIs) for colistin was 1.45 (95% CI 1.16, 1.82). In the secondary meta-analysis, the pooled RR among studies that reported adjusted HR of Colistin to polymyxin B was 1.58 (95% CI 1.35 to 1.81).

Conclusion: The meta-analysis suggests that colistin is associated with a higher nephrotoxicity risk compared to polymyxin B. Considering renal safety, polymyxin B should be regarded as the preferred option for patients with infections treated by polymyxins therapy.

264 Rapid advice guidelines for the pharmacological management of human albumin in patients with liver cirrhosis

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Background: Human albumin (HA) is widely used in hepatology due to support from international scientific societies for the treatment or prevention of severe complications in cirrhosis. However, no formal guidelines exist regarding its use in China, and in many clinical situations, limited evidence is available due to its high cost and the use of alternative treatments.

Objectives: The Chinese Hospital Association, Chinese Society of Clinical Pharmacy and Chinese Society of Hepatology, Chinese Medical Association have developed evidence-based, rapid advice guidelines for the pharmacological management of HA in patients with cirrhosis to implement appropriate HA use.

Methods: We referred to the WHO Handbook for Guideline Development and used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system to rate evidence quality and grade the strength of recommendations according to evidence quality, benefits, harms, burdens, costs, and values. We used a Delphi vote to formulate these recommendations.

Results: These guidelines present practical clinical recommendations for the use of HA in patients with cirrhosis.

Conclusions: We developed the first evidence-based, rapid advice guidelines for the pharmacological management of HA in patients with liver cirrhosis to facilitate appropriate HA use by clinicians and pharmacists in China.

265 Menatetrenone (vitamin K2) in the management of osteoporosis: rapid health technology assessment

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Objectives: To evaluate the efficacy, safety and cost-effectiveness of menatetrenone (vitamin K2), and to help health care professionals and decision maker to better understand the evidence of menatetrenone.

Methods: A comprehensive literature search was performed in PubMed, Cochrane library, Embase, CNKI, CBM, WanFang and clinicaltrials.gov. For HTAs, systematic review and meta-analyses and cost-effectiveness studies, descriptive analysis was performed. Meta-analysis was performed for randomized controlled trials (RCTs).

Results: Twenty-three studies were eventually included, of which 1 was health technology assessment (HTA), 1 was systematic review, 1 was cost-effectiveness study and 20 were RCTs. Compared with placebo or no additional drugs, menatetrenone decreased undercarboxylated osteocalcin (ucOC) and increased bone mineral density (BMD) significantly. Also, there was a decreased trend towards incidence of fracture and vertebral fracture. Compared with calcium or alfacalcidol, menatetrenone significantly decreased ucOC, however, there was no significant decrease in fracture risk. Menatetrenone was associated with no significant decrease in fracture risk compared with etidronate. For safety outcomes, menatetrenone was associated with a significant higher incidence of adverse events compared with placebo. There was no significant difference in adverse events compared with active drugs. No coagulation disorder events have been reported in the trials available. Concerning cost-effectiveness, a study in Canada demonstrated that vitamin K2 as add-on treatment to vitamin D3 and calcium was a cost-effective intervention.

Conclusion: Menatetrenone decreases ucOC significantly compared with controls and safety is relatively good. Further research on the efficacy of menatetrenone on fracture and cost-effectiveness in China is warranted.

266 Association of hormone replacement therapy with risk of dementia in post-menopausal women: a meta-analysis for observational study

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Objectives: Some evidences indicated that hormone replacement therapy (HRT) was associated with a significantly lower risk of dementia. The purpose of this meta-analysis is to evaluate the association between HRT and lowered risk of dementia in post-menopausal women.

Methods: The information is obtained mainly from the following sources: PubMed, Embase, Wiley Online Library, Lippincott Williams & Wilkins, ClinicalKey, Google Scholar, WANFANG MED ONLINE and Airiti Library for all-language publications in February 2018, all studies included thirteen observational studies in 1994 to 2017, and 83 to 230,580 all participants in Europe, United States of America and Asia with follow-up duration of 6 months to 20 years. The main outcome used both fixed and random effect models to calculate pooled relative risks and to estimate statistical heterogeneity. All data were analyzed using Review Manager 5.3 and STATA 14.0 statistical analysis software.

Results: The pooled relative risks of dementia in HRT exposure as compared with non-exposure were 0.76 (95% CI 0.55-1.06) in random effect model, with evidence of heterogeneity (I^2=98.3%, P<0.001).

Conclusion: Findings of the meta-analysis indicate that HRT appears to be lowered risk of dementia in post-menopausal women.

267 Levetiracetam for epilepsy: an evidence map of efficacy, safety and economic profiles

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Objective: To evaluate clinical efficacy, safety and economics of levetiracetam (LEV) for epilepsy and provide scientific information for clinical practice and decision-making for rational selection of medication.

Methods: PubMed, Scopus, the Cochrane Library, OpenGrey.eu and Clinicaltrials.gov were searched for systematic review (SR), meta-analysis, randomized controlled trials (RCTs), observational studies, case reports and economic studies. The search period was from Jan 2007 to April 2018. The evidence map is based on the above included studies. We used a bubble plot to graphically display clinical topics, literature size, number of studies, and a broad estimate of effectiveness and safety.

Results: A total of 14803 records were obtained. We included 30 SR/meta-analysis, 34 RCTs, 19 observational studies, 58 case reports and 2 cost-effectiveness study after the screening process. Included meta-analysis and meta-analysis of included RCTs indicated that LEV increased rates of seizure freedom compared with placebo (OR=5.42, 95%CI 3.27,8.98), and was similarly efficacy with CBZ (OR=0.76, 95%CI 0.50 to 1.16), OXC (OR=1.34, 95%CI 0.34 to 5.23), PB (OR=1.20, 95%CI 0.51 to 2.82) and LTG (OR=1.22, 95%CI 0.90 to 1.66). LEV also increased rates of ≥50% responder rates compared with placebo (OR=3.20, 95%CI 2.27 to 4.52). Meta-analysis of included RCTs indicated that, LEV decreased discontinuation due to AEs compared with CBZ (OR=0.52, 95%CI 0.41 to 0.65). Two SRs and two observational studies indicated that LEV had a low malformation rate and intrauterine death rate for pregnant women. A SR and one observational study indicated low risk of cognitive side effects of LEV. But psychiatric and behavioral side effects of LEV could not be ruled out. Two cost-effectiveness evaluations for refractory epilepsy showed US$ 76.18 per seizure-free day (SFD) gained in Canada and US$ 44 per SFD in Korea.

Conclusions: Levetiracetam is an effectiveness medication for epilepsy, had an advantage for pregnant women and in cognitive functions. LEV is cost-effectiveness under certain conditions.

268 Evaluation of current guidelines for using antifungal agents in adult non-neutropenic critically ill patients: using the AGREE II instrument

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Objective: There are numerous clinical practice guidelines (CPG) for the use of antifungal agents in non-neutropenic critically ill patients. The recommendations in these CPGs may differ because they were developed using different methodologies. The objective of this study was to systematically appraise CPGs for this indication.

Methods: We systematically searched the literature to identify CPGs published within the last ten years on antifungal treatments applied to non-neutropenic critically ill patients. We assessed the quality of each guideline using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (six domains). We extracted the recommendations of antifungal prophylaxis, empirical or pre-emptive, and targeted treatment.

Results: There were 21 CPGs included. Most were for invasive (n=15) or intra-abdominal candidiasis (n=3) and most were from Europe (n=10). The mean overall assessment score was 58% (SD=24%). The domain - clarity of presentation - had the highest scores (88%, SD=13%) while the domain - Applicability - had the lowest scores (17%, SD=15%). Only five CPGs had a quality score ≥80% and only one had scores >70% in all domains except for Applicability. Most CPGs gave detailed recommendations on antifungal prophylaxis (n=10), empirical or pre-emptive treatment (n=17) and targeted candidiasis treatment (n=19). Fluconazole was recommended as the only initial prophylaxis drug in all seven of the included CPGs which recommended a specific drug. Echinocandin was recommended as the initial drug in all 16 CPGs supporting empirical/pre-emptive treatment and 18 CPGs for targeted candidiasis, respectively.

Conclusion: The methodological quality of CPGs for the use of antifungal agents in non-neutropenic critically ill patients is suboptimal. These findings highlight the need for improved or optimally reported guideline development processes in the future, and further improvement in the applicability domains of the AGREE II criteria would strengthen the quality of the CPGs.

269 Review of the drug utilization researches of outpatient antibiotics in China

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Objective: This study aimed to review and describe the characteristics of drug utilization researches (DURs) of outpatient antibiotics in China.

Methods: PubMed and Chinese Journal Full-text Database (CNKI) were searched from January 1, 2013 through December 21, 2017. Observational studies of outpatient antibiotic use in China were included.

Results: A total of 300 observational researches of outpatient antibiotic use in China were included in the study, among which 86.3% were descriptive ones. There were 52 multicenter researches, only taking a proportion of 17.3%, and of which 78.8% were conducted in primary healthcare centers. In addition, only 12 (4%) researches included hospitals in more than one province of China. Over 76% of all the researches and over 63% of the multicenter ones included less than 10,000 prescriptions. The most common used measurement index in DURs of outpatient antibiotics was the rate of antibiotic prescriptions, reported in 83.7% of all the included studies, followed by the composition of antibiotic use (45% reported), the percentage of antibiotic combined therapy (39.3% reported), the percentage of appropriate use of antibiotics (37.4% reported). Only 16.3% of the researches used the Anatomical Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) classification developed by WHO and less than 5% researches analyzed and reported the antibiotic costs of outpatients and its percentage in the total drug costs or total prescription costs in China. Furthermore, there were large variances of measurement indexes across studies and a decreasing tendency in the number of researches of outpatient antibiotic use in China in recent years was observed.

Conclusions: Drug utilization researches of outpatient antibiotics in China were not high-quality, with the characteristics of ordinary methodologies, simple analysis, insufficient and unrepresentative samples. Further and deeper analysis of outpatient antibiotic use in China at the national level are needed in the future.

270 Outpatient parenteral antibiotic use in China: a nationwide descriptive analysis

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Objective: To assess the parenteral treatment of outpatient antibiotic use in Chinese hospitals.

Methods: All the outpatient prescriptions from 187 hospitals in 31 provinces, autonomous regions, or municipalities in China, between Oct 1, 2014 to Dec 31, 2016 were extracted. The Anatomical Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) classification was used for the calculation of antibiotic consumption. Outpatient use of parenteral antibiotics for systemic use (J01) was analyzed and expressed as percentage of total antibiotic prescriptions and average DDDs per prescription.

Results: There were 12,768,002 prescriptions with at least one antibiotic, accounting for 9.2% of all the outpatient prescriptions. 26.1% of antibiotic prescriptions were for parenteral treatment and the numbers of DDDs of parenteral antibiotics per prescription were 1.8. Parenteral treatment of antibiotics took a larger proportion in secondary hospitals (37.83%) than in tertiary hospitals. Hospitals in northeast (39.09%) and east (32.99%) regions of China used a higher percentage of parenteral antibiotics than that in the west and south regions. In addition, female patients (27.23%) and children under 6 years (33.3%) used an obviously larger proportion of parenteral antibiotics. In total, there were 94 unique parenteral antibiotics (ATC-5 level) affiliated to 8 pharmacological subgroups (ATC-3 level) and 22 chemical subgroups (ATC-4 level). Fluoroquinolones (J01MA), imidazole derivatives (J01XD), second-(J01DC) and third-(J01DD) generation cephalosporins, and aminoglycosides (J01G) were the most common used parenteral antibiotics in China, accounting for 21.0%, 18.4%, 15.2%, 10.7% of all prescribed parenteral antibiotics, respectively. Furthermore, there was a significant decreasing tendency in the percentage of parenteral antibiotic use with a reduction of 0.73% per month.

Conclusions: Use of parenteral antibiotics was still common in Chinese hospitals and obviously higher than that of some developed countries. Otherwise, parenteral treatment of antibiotics in outpatients was decreasing, indicating the gradual effective control of parenteral antibiotic use in China.

271 Outpatient quinolone use in China

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Objective: To describe the outpatient quinolone use in Chinese hospitals and to analyze the trends and compositions of quinolone use over time.

Methods: A total of 139.18 million prescriptions from 187 hospitals in 31 provinces of China mainland from Oct 1, 2014 to Dec 31, 2016 were extracted. The ATC/DDD (Anatomical Therapeutic Chemical Classification/Defined Daily Dose) system was used for the classification of antibiotics and calculation of antibiotic consumption. The trends over time, seasonal variations and compositions of quinolone use were analyzed using multilevel models.

Results: Every 2.19 million prescriptions contained at least one quinolone, accounting for 17.15% of the antibiotic prescriptions. On average, outpatients consumed 9.16 DDDs per 100 patient-visits (DPV), accounting for 15.4% of total antibiotic consumption. The second-generation quinolones (76.3%) took the biggest proportion of the total use. The third-generation quinolones (18.2%) were the second most widely used. Furthermore, norfloxacin (5.2%), one of the second-generation quinolones, ranked third.
Tertiary hospitals used more third-generation quinolones than secondary hospitals, while secondary hospitals used more first-generation ones than tertiary hospitals. Western regions used more third-generation quinolones than other regions, meanwhile, Central regions used more first-generation quinolones than other regions. With the ascent of the tiers of cities, more first-generation quinolones and less third-generation quinolones were used.
Recent years saw a significant decrease in outpatient quinolone use, while the seasonal variation was not evident. With the increase of total quinolone use, more second-generation quinolones were used compared to the first- and third-generation ones. In addition, relative use of third-generation quinolones was higher with respect to the use of first-generation quinolones where the total quinolone use was high.

Conclusion: Although there is a decreasing tendency, quinolone use is still high in China. Proper measures are needed to control the quinolone use of Chinese outpatients.

272 Prescription drug among patients with dengue fever in Japan: results from National Claims Database

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Aim: WHO published the clinical guideline for dengue in 2009, and the Japanese guideline was published in 2014. Both guidelines recommend to use acetaminophen, inhibit to use Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), but show no evidence of using platelet transfusion for dengue patients. As they induce bleeding, use of NSAIDs might lead dengue fever (DF) patients to develop dengue hemorrhagic fever (DHF). The Japanese National Claims Database (NDB), one of the most suitable databases for pharmacoepidemiologic research, has the data of all prescriptions covered by public medical insurance schemes. This research aims to clarify prescription drugs for dengue patients in Japan using NDB.

Methods: We had claims that had DF or DHF extracted from NDB from 2011 to 2015. We categorized prescribed drugs into acetaminophen, NSAIDs, and platelet transfusion and counted the number of patients who received drugs by each category. We used Fisher's exact test to compare usage of each category between DF and DHF patients.

Results: The number of DF and DHF patients between 2011 and 2015 was 1306 and 64, respectively. Among them, 719 DF patients (55.1%) and 34 DHF patients (53.1%) received acetaminophen (p=0.798), 169 (12.9%) and 12 (18.8%) NSAIDs (p= 0.185), and 17 (1.3%) and 11 (17.2%) platelet transfusion (p<0.001), respectively.

Conclusion: Acetaminophen was used more than NSAID. Nevertheless, more than 13% of the dengue patients received NSAIDs. The difference of using NSAIDs between DF and DHF patients was not statistically significant. However, since the study used the data of all dengue patients in Japan during the study period, the result indicated that use of NSAIDs might have caused some of the DF patients to develop DHF. Despite no evidence for its efficacy, 17.2% of DHF patients received the platelet transfusion. More efforts are needed to publicize the guideline to treat dengue patients appropriately.

273 Prescription patterns and appropriateness of topical mupirocin in ambulatory care using the Korean National Health Insurance Claims Database

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Aim: Mupirocin, a topical antimicrobial agent has been used for patients with methicillin-resistant Staphylococcus aureus and recently mupirocin resistance was issued in some studies. The objective of this study was to analyze prescription patterns of topical mupirocin, to evaluate appropriateness of prescriptions in the ambulatory setting, and to compare frequency of mupirocin usage in South Korea with that in United States.

Methods: Topical mupirocin prescription patterns (the number of prescription and a prescription period), and appropriateness of prescription (including a prescription rate over 10 days, a repeat prescription rate within 30 days and a prescription rate within labeled indications) were analyzed using the 2012 Health Insurance and Review and Assessment service-National Patient Sample dataset of South Korea. The National Ambulatory Medical Care Survey dataset was used to quantify topical mupirocin prescription in United States for comparison.

Results: In South Korea, the prescriptions rate for use over 10 days was 3%, the repeat prescription rate within 30 days was 8.87% and the prescription proportion within labeled indications was 33.84%. The most frequent diagnostic code was nonbacterial infection. The prescription rate per 1000 population of topical mupirocin in South Korea was calculated to be 46.07, whereas in United States was calculated to be 13.10.

Conclusion: Topical mupirocin has been used frequently and inappropriately, so further studies are required to investigate the rationale behind such prescribing mupirocin patterns.

274 Real world second- and later-line treatment regimens for relapsed/refractory small cell lung cancer in Germany and the United States

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Aim/Objective: There are no optimal drugs for the treatment of relapsed/refractory small cell lung cancer (SCLC). Topotecan is the only approved second-line agent, and no drug or combination regimen is approved in the third- or later-line setting. The purpose of this study was to describe and compare the use of second- and later-line treatment regimens for SCLC in routine clinical practice in Germany and the United States (US).

Methods: The analysis of the drug utilization in Germany was based on extraction of retrospective data from medical records at 36 oncological practices/centers using an eCRF (2010-2016). Of 160 SCLC patients who received second-line treatment, 46, 12, and 3 received the third-, fourth- and fifth-line, respectively. The analysis in the US was based on Optum EHR data from a network of healthcare provider organizations (2007-2016). Of 1,211 patients who received second-line treatment, 428, 138, 45, 17, 5, 1 received third-, fourth-, fifth-, sixth-, seventh- and eighth-line, respectively.

Results: In 2nd line, the most frequently prescribed regimens were topotecan as single therapy (41%), a combination of doxorubicin+cyclophosphamide+vincristine (ACO) (14%), and carboplatin+etoposide (6%) in Germany and were topotecan single (31%), carboplatin+etoposide (21%), and paclitaxel (8%) in the US. In ≥ 3rd line, the most frequently prescribed therapies were topotecan (23%), ACO (16%), paclitaxel single (7%) in Germany and were topotecan (24%), paclitaxel (16%), gemcitabine (10%), docetaxel (8%), and carboplatin+etoposide (8%) in the US.

Conclusion: This analysis provides a unique international comparison of the treatment regimens for relapsed/refractory SCLC. Topotecan has been the main 2nd+ line of treatment for SCLC for the last decade in both Germany and the US. Doxorubicin-cyclophosphamide-vincristine combination therapy was prescribed more commonly in Germany than in the US whereas carboplatin+etoposide and paclitaxel were prescribed more commonly in second- and later-lines respectively, in the US than in Germany.

275 Treatment pattern of patients with locally advanced and metastatic melanoma in a real-world setting in China

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Objective: In China, treatment options for late-stage melanoma, particularly for second-line (2L) therapy, are limited. This retrospective, observational study used electronic medical records (EMRs) of patients (pts) with melanoma treated at Beijing Cancer Hospital (BCH) to describe the treatment pattern in locally advanced, metastatic melanoma in China.

Methods: All adult pts with unresectable stage III or IV melanoma who initiated treatment between Jan 1, 2014, and Dec 31, 2015, were eligible. In total 248 eligible patients were identified and included in this study. Trained researchers abstracted relevant information from the EMR database.

Results: Of 248 patients, almost all (~95%) had stage IV melanoma; 91.4% of them had a history of chemotherapies and 59.5% received surgeries prior to being treated at BCH. Within the treatment period at BCH, 221 received first-line (1L) therapy and 116 received 2L therapy (89 received both). About 92% of 1L therapies and 87% of 2L therapies were combination. The most common 1L regimens were dacarbazine + cisplatin + recombinant human endostatin (RHE) (36.7%) and paclitaxel + carboplatin + bevacizumab (22.2%). The most common 2L regimens were paclitaxel albumin + carboplatin + bevacizumab (22.4%), paclitaxel + carboplatin + RHE (15.5%) and paclitaxel albumin + cisplatin + RHE (12.1%). Approximately 40% of patients had a ≥3 month duration of 1L therapies; only 9.5% of patients had a duration ≥6 months. Fewer patients on 2L therapies had a duration of treatment ≥3 months (27.6%), although the duration ≥6 months was the same (9.5%). The most common reasons for treatment discontinuation were disease progression (50.7% for 1L, 59.5% for 2L) and withdrawal by patients without reasons (18.6% for 1L, 24.1% for 2L).

276 Cost effectiveness analysis of pembrolizumab in cancer therapy: a systematic review

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Objective: To assess the cost effectiveness of Pembrolizumab in cancer therapy.

Methods: A systematic search for randomized controlled trials was done in relevant databases. Studies compared PEM to other treatment types such as ipilimumab and standard of care chemotherapy.

Results: Patients treated with 1st or 2nd line Pembrolizumab relative to Ipilimumab had increased life expectancy, delayed tissue progression and higher overall costs. Pembrolizumab tested against standard of care chemotherapy as 1st line agent (for PDL-1 positive patients) increased quality assurance life years (QALY) compared to paclitaxel, carboplatin, pemetrexed, cisplatin, and gemcitabine. PEM had a high per patient cost of $145,010 and $130,511 in the treatment of melanoma and NSCLC compared to other agents such as Ipilimumab and nivolumab. Increase in life expectancy was up to 1.57 undiscounted life-years. The QALY threshold ranged from $50,000 to $100,000.

Conclusion: Pembrolizumab has a high drug acquisition and disease management cost but is more cost effective relative to other immunotherapies. Treatment with pembrolizumab was most cost effective when limited to 2 years. Costs increased when treatment went beyond two years. More studies should be conducted in the US setting to further conclude the cost-effectiveness of pembrolizumab in the treatment of cancer.

277 Adherence and concomitant medication use among persons on warfarin therapy: insight from large pharmacy dispensing database in Japan

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Aim: Warfarin is a drug used for anticoagulation management, with narrow therapeutic range and multiple drug-drug interactions. Adherence and concomitant medication use are thus fundamental to the efficacy and safety of warfarin therapy.

Methods: We retrospectively analyzed data from there large-scale pharmacy chains in Japan in 2012. All adult persons (≥ 20 years old) at least one dispension records of warfarin were included. We examined patient demographic data, adherence as measured by medication possession rate (MPR) and co-dispension focusing on the number of concomitant dispension and concurrent use of medication with increased bleeding risk. The thresholds of underadherence and overadherence were set at <0.9 and >1.1 in this study, considering the narrow therapeutic window.

Results: We reviewed data of 443,007 warfarin dispension records among 71,340 individuals (median age, 73 years; 62% male). The MPR was 1.0 (interquartile rage: 0.96-1.0), and underadherence and overadherence were found in 16.3% and 1.9% of the population, respectively. The number of co-dispensed drug was a median of eight at each encounter, which did not differ among different age-groups. Drugs associated with higher bleeding risk were dispensed in 40.0 % of encounters, and accounted for the 16.4% of all co-dispensed drugs.

Conclusion: Adherence assessed by MPR was overall optimal among the study population in Japan, even defining the strict cut-off value. However, polypharmacy was common in all age-groups and medications related to higher bleeding risk profile were often co-dispensed with warfarin. Future research addressing how these dispension patterns affect patient outcome would be of relevance.

278 Utilization of the beliefs about medicine questionnaire and prediction of medication adherence in China: a systematic review and meta-analysis

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Objective: This study aimed to investigate utilization of the Beliefs about Medicines Questionnaire (BMQ) in China.

Methods: Searches were performed in PubMed, EMBASE, PsycINFO, CNKI and WANFANG DATA for studies published between January 1997 and October 2017, measuring Chinese people's medicine beliefs using BMQ translations. Two independent reviewers assessed 3528 records retrieved. The data extraction and quality assessment were finished independently as well. Random-effects meta-analysis was used to test whether specific beliefs about medicines predicted medication adherence.

Results: Thirty-six eligible articles were identified, of which sample sizes ranged from 48 to 820, involving 8200 participants. Ten studies reported acceptable reliability for BMQ subscales (Cronbach's □> 0.50). Three most commonly used Chinese version of the BMQ were specific to patients with cardiovascular disease, depression, and breast cancer. Nine articles were included in the meta-analyses. Adherence was significantly correlated with necessity beliefs (pooled r=0.21 95% confidence interval (CI): 0.07, 0.34), concerns (r= -0.40, 95% CI: -0.48, -0.32), and the necessity-concerns differential score (r= 0.29, 95% CI: 0.18, 0.40). There was moderate, significant heterogeneity between studies for necessity beliefs (I2=67%, p=0.006) and concerns (I2=74%, p=0.0007).

Conclusion: The BMQ has been widely used in China and appears to be reliable. As in other countries, the BMQ appears to be a useful tool for assessing medication beliefs in China. The Necessity-Concerns Framework is a useful conceptual model to explain medication adherence.

279 Drug utilization of anti-diabetic medications in patients with type 2 diabetes mellitus from 2012-2015 in Beijing, China

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Objective: The present study aimed to characterize the utilization of anti-diabetic medications in type 2 diabetes mellitus (T2DM) patients in Beijing China, further to identify T2DM pharmacological treatment patterns in the real world.

Methods: Beijing Urban Employee Basic Medical Insurance database (2012-2015) was used to conduct this retrospective study. T2DM patients were identified in 2012 and followed until 2015. Patterns of pharmaco-therapy were examined including the usage of oral hypoglycemic agents (OHAs), insulin and lifestyle education only. The proportion of patients treated with different types of anti-diabetic drugs and drug combinations were tabulated and ranked overall.

Results: The cohort consisted of 27,848 patients who were dispended 536,438 prescriptions for anti-diabetic drugs, 49% (n=13,518) were male and 97% were aged 40 and above (mean 62.28±11.40 years).
Of all the patients analyzed 95% (n=26,401) received at least one type of drug treatment rather than lifestyle intervention only (n=1,447, 5%). It was found 50% (n=14,003) were treated with OHAs alone, while 41% (n=11,429) had OHAs combined with insulin. 3% (n=969) were treated with insulin or insulin analogs only.
Among patients treated with anti-diabetic drugs, the most commonly prescribed drug was acarbose (n=19,978, 72%), followed by metformin (n=16,009, 57%) and sulphonylureas (n=12,852, 46%). Mono pharmaco-therapy was the main pattern for 25,359 patients (91%). As to the combination therapy, dual pharmaco-therapy was prescribed in 67% (n=18,749) of patients, while 26% (n=7,244) were given a three-agent combination. The combination of metformin and acarbose was used most frequently, with around 21% of patients (n=5,755).

Conclusions: In Beijing China, almost all the T2DM patients were treated with anti-diabetic drugs, especially with OHAs only. Acarbose was the most commonly used drug, while metformin, as the first-line therapy recommended in diabetes clinical guideline, was not used widely in China.

280 Drug utilization research of antihypertensive drugs for hospitalized patients with hypertension in Shenyang

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Objective: To evaluate the drug utilization of antihypertensive drugs by hospitalized patients with hypertension in Shenyang for promoting the level of rational drug use.

Methods: From January 1, 2011 to January 1, 2016, data of 4000 hospitalized patients with hypertension were stratified randomly selected from 2 third-grade class-A hospitals in Shenyang. The data of drug utilization of antihypertensive drugs was evaluated.

Results: The most widely used antihypertensive drug was amlodipine (8.02%, 1044/13016). The maximum DDDs was 19326.69 (Valsartan Amlodipine). The maximum drug utilization index was 1.85 (valsartan amlodipine), and the minimum drug utilization index was 0.47 (Felodipine). The drug utilization index was close to 1 as follows: ramipril (1.00), losartan (1.02), and irbesartan (0.96).

Conclusions: The utilization of antihypertensive drugs was more rational for inpatients with hypertension in Shenyang.

281 Joint considerations of safety and efficacy for expansion cohorts in phase I drug trials

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Aim: Phase I clinical trials increasingly incorporate dose-expansion cohorts (DECs), reflecting a growing demand to acquire more information about investigational drugs. Protocols commonly fail to provide a sample-size justification or analysis plan for the DEC. In this study, we aim to develop a framework for the design of DECs that seek to evaluate toxicity and efficacy of an investigational drug.

Methods: We use the traditional 3+3 design for the dose-escalation portion of the trial to identify a maximum tolerated dose (MTD) for the drug. We use the 80% lower confidence bound and the 90% upper confidence bound for the response and toxicity rates, respectively, as decision thresholds for the dose expansion stage. We calculate the operating characteristics according to prespecified thresholds for minimum and desirable response rates as well as maximum and safe DLT rates.

Results: We apply our framework to specify various DEC designs. The design comprises three components: 1) the number of subjects enrolled at the MTD, 2) the minimum number of responses necessary to indicate provisional drug efficacy, and 3) a stopping bound for toxicity that indicates the minimum number of dose-limiting toxicities (DLTs) at which the drug is deemed unsafe. We demonstrate our method in an application to a cancer immunotherapy trial.

Conclusions: Our simple and practical tool enables creation of DEC designs that appropriately address the safety and efficacy objectives of the trial.

282 A nationwide follow-up study to investigate the patterns of use of long-acting bronchodilators in patients with COPD in New Zealand

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Aim/Objective: Although a number of recent studies have shown an inconsistency between prescribing practices and chronic obstructive pulmonary disease (COPD) treatment guidelines, none of them have examined longitudinal patterns of use of long-acting beta2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapy across an entire study. In this research we aimed to describe treatment patterns in new users of long-acting bronchodilators using New Zealand national health and pharmaceutical dispensing data.

Methods: The study cohort included all patients who were first dispensed LABA and/or LAMA therapy for COPD between 1 February 2006 and 31 December 2013 in New Zealand. The treatment patterns were summarized using sunburst plots, Kaplan-Meier curves and sequence index plots.

Results: A total of 83435 patients were included in the cohort. LABA with an ICS was the most commonly dispensed regimen at cohort entry. The next most common regimens were LABA monotherapy and LAMA monotherapy. In addition, ICS monotherapy was common and inconsistent with guidelines. Many patients were on multiple regimens and periods of non-use are common.

Conclusions: We have found that prescribing practices do not follow COPD treatment guidelines and further work needs to be carried out to address this discrepancy.

283 Drug utilization trend of monoclonal antibody in China: 2013-2016

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Aim: This study aimed to characterize the national drug utilization trend of monoclonal antibody (mAb) in China during 2013 to 2016, expecting to provide reference for drug therapy and health policy about mAb utilization in China.

Methods: This study analyzed the data extracted from the CHIS database which covered hospitals in 30 provinces (municipalities) in China. Sales value and units of marketed mAbs were analyzed in an evolutionary and descriptive way.

Results: For the 18 mAbs (10 imported; 8 domestic) included, the total sales value increased from 2.21 billion CNY to 2.99 billion CNY; the total sales volume increased from 0.96 million units in 2013 to 1.58 million units in 2016. Among the 18 mAbs, rituximab was the leading product in market, followed by trastuzumab. The imported mAbs dominated the market in terms of market share and sales value, while domestic mAbs were increasing their utilization in medical institutions. The targeted indications included lymphoma, metastatic breast cancer, rheumatic arthritis, metastatic colorectal cancer, nasopharyngeal carcinoma, prevention of acute renal allograft rejection, primary liver cancer, and macular.

Conclusion: The mAb products has been increasingly used by Chinese medical institutions, which generally following the international trends. Further pharmacoepidemiology study of mAbs in China needs to be conducted to provide better drug access and deeper instructions for clinical application in China.

284 Discharge prescribing in older adults with type 2 diabetes hospitalised for diabetes-related complications

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Aim: Recent guidelines recommend relaxing glycaemic goals for frail older adults with type 2 diabetes mellitus (T2DM). We examined the association between age and discharge prescribing of diabetes medications in people hospitalised for diabetes-related complications.

Methods: This was a cross-sectional study of 4130 adults with T2DM admitted to six hospitals in Melbourne from 2012-2016 with a primary diagnosis of a diabetes-related complication. Logistic regression was used to examine the association between age and discharge prescribing of diabetes medications, adjusted for demographic and health factors. Separate models were conducted for all diabetes medications, insulins and oral medications.

Results: Overall, 756 (18.3%) people were aged ≥85 years. Of those, 34% were not prescribed any diabetes medications, 18% were prescribed only insulin, 38% were prescribed only oral medications, and 22% were prescribed both insulin and oral medications. The most prevalent oral medications in people aged ≥85 years were sulfonylureas (32%) and metformin (27%), with 15% of people prescribed multiple oral medications. People aged ≥85 had lower odds of being prescribed insulin (odds ratio [OR] 0.47; 95% confidence interval [CI] 0.36-0.61), oral medications (OR 0.67; 95%CI 0.55-0.83), or both insulin and oral medications (OR 0.38; 95%CI 0.29-0.50) than not being prescribed diabetes medications, compared to those <85 years. Among people prescribed insulin and people prescribed oral medications, people aged ≥85 years were less likely to be prescribed multiple medications compared to those aged <85 (≥2 insulins vs. one insulin OR 0.48; 95%CI 0.32-0.72; ≥3 vs 1-2 oral medications OR 0.35; 95%CI 0.16-0.77).

Conclusion: People aged ≥85 years were less likely to be prescribed diabetes medications, and when prescribed medications, were prescribed less intensive regimens than those aged <85 years. Further research is needed into the risks and benefits of the relatively high prevalence of sulfonylureas and apparent avoidance of metformin in this age group.

285 Hypoglycaemia hospitalisation cost and length of stay in patients with diabetes mellitus: a cross-sectional study

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Aims: to estimate the mean length of stay and hospitalisation cost of hypoglycaemia, and to identify their determinants of variation among patients with diabetes mellitus.

Methods: a cross-sectional study was conducted in Jordan using inpatients records of two private hospitals for patients with diabetes mellitus, who have been hospitalised due to hypoglycaemia between January 2009 and May 2017. All hospitalisation costs were inflated to costs in 2017. Hospitalisation cost was estimated from patients perspective in Jordanian dinars (JOD). Spearman's correlation coefficient and the Mann-Whitney test were used to analyse the association between independent variables and hypoglycaemia related hospitalisation cost and length of stay. Multiple linear regression analysis was used to identify predictors of hypoglycaemia hospitalisation cost and length of stay.

Results: during the study period a total of 126 patients with diabetes mellitus were hospitalised due to an incident of hypoglycaemia. The mean patient age was 64.2 (SD= 19.6) years old, of which half were male. The median length of hospital stay was 2 days (IQR= 2 days). The median cost of hospitalisation for hypoglycaemia was 160.0 JOD ($225.7) (IQR= 211.7 JOD, $298.6). We found that Glasgow coma score positively associated with length of stay (0.345, $p \leq 0.01$), and older age was correlated with higher hospitalisation cost (0.207, $p \leq 0.05$). Patients with family history of diabetes and who were dependent in their daily activities had a longer length of stay ($p \leq 0.01$), and higher hospitalisation cost ($p \leq 0.01$).

Conclusion: hospitalisation due to hypoglycaemia among patients with diabetes mellitus represents a substantial economic burden within hospital settings. Healthcare professionals should give more attention to this adverse drug event to decrease the burden of its associated cost.

286 A review of 2017 "real world" evidence literature in Asia

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Aim/Objective: The term "real world evidence" (RWE) has become common in recent years. This review's objective was to evaluate 2017 RWE publications in Asia compared with the rest of the world (ROW).

Methods: We reviewed English language 2017 titles and abstracts in Pubmed and Embase for the term "real world." Abstracts were categorized into "Asia" (including Australia) and ROW. The following were also extracted: therapeutic area, exposure type, study design, primary outcome, and data source. Descriptive analyses were performed.

Results: There were 1045 hits for "real world" publications in 2017. Of these, 315 were excluded because they lacked an abstract (n=93) or were not related to provision of health care (n=222); 730 remained in the analysis. Of these, 128 were conducted in Asia, 329 were only ROW, and 273 could not be categorized.
In Asia, most studies were retrospective (59%) vs prospective (40%); 63% evaluated drugs and 14% devices. Data sources were medical records (34%), primary data collection (31%), claims data (9%), registries (11%), and other/not reported (16%). Effectiveness was assessed in 31% of studies; safety in 18%; and treatment patterns in 11%. Two-thirds focused in 3 therapeutic areas: cardiovascular (30%), oncology (20%), and infectious disease (17%).
Compared with ROW, studies in Asia were more likely to be prospective; use primary data; and assess cardiovascular exposures. Studies in Asia were less likely to evaluate drugs; use claims data; and assess safety or effectiveness. Otherwise, RWE in Asia was similar to ROW.

Conclusions: RWE is needed across geographies to demonstrate utilization, safety and effectiveness of health technologies outside clinical trials. Clarity in reporting is needed. Publications from 2017 indicate that many studies are being conducted in Asia and reported in the English literature. Opportunities exist for increased study of drugs, use of secondary data sources, and evaluation of safety and effectiveness outcomes.

287 Empirical investigation on Chinese pharmaceutical listed companies' environmental disclosure

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Objective: To evaluate the quality of Chinese listed pharmaceutical companies about their environmental disclosure by analyzing their 2015-2017 annual reports and corporate social responsibility (CSR) reports.

Methods: All Chinese pharmaceutical listed companies are selected by the classification of China Securities Regulatory Commission (CSRC) website. 2015-2017 annual reports and CSR reports disclosed by the 121 sample companies were manually collected from the website of Shanghai Stock Exchange, Shenzhen Stock Exchange and cninf, which is CSRC designated information disclosure website.

We use a Content Analysis to quantify the situation of corporate environmental disclosures. Considering the GRI Standards and the actual situation in China, we design an Environmental Performance Assessment Indicator System to reflect the environmental performance in Chinese pharmaceutical industry.

Results: (1) According to our Environmental Performance Assessment Indicator System, from 2015 to 2017, the average score of Chinese pharmaceutical listed companies is only 4.36, 4.82 and 6.10* respectively. *: Full score is 39
(2) In 2015-2017, the percentage that the 121 companies disclosed CSR reports is 28.10%, 29.75% and 29.75% respectively.
(3) 18/37 companies, who have disclosed their environmental information, are state-owned, and their average environmental performance point (10.78) is higher than private companies (9.25).
(4) In the 7 sections of our system, companies get the lowest score at the part of Environmental Costs with the average percentage of total score is 5.73%, and get the highest at Environmental Management with 26.43%.

Conclusion: There is little research focus on Chinese pharmaceutical industry as a whole field to examine cooperate environmental disclosure. Our study finds the unsatisfactory performance of Chinese pharmaceutical listed companies. However, their scores rise annually in 2015-2017, which means that Chinses pharmaceutical industry has paid attention to environmental disclosure. With related law published, especially New Environmental Protection Law introduced in 2015, companies should disclose environmental information positively.

288 Can Health care utilization of 1/5 chinese be protected? — analysis of inpatients of floating population in Jiangsu

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Objective: To understand the status of in-patient health service utilization of floating population, to find out whether the rights of floating population hospital health services can be guaranteed.

Method: Use the data from National Floating Population Health Survey of Health Statistics involving 12000 questionnaires which investigated health care utilization of inpatients of floating population in Jiangsu Province. Filter 422 cases who have received hospital health care in the last year.

Results:
1. Up to 29.41% of inpatients' reimbursement is not covered.
(1) Half of them do not have any kind of insurance;
(2) The dilemma that inpatients can't get reimbursement in the city they are treated blocked 25% out-of-pocket inpatients.
2. Hospitalization expenses of 11.09% inpatients are full covered, ranking second.
3. The reimbursement rates of other 10 groups didn't exceed 10%.
4. The mean value (42.5%) of all inpatient reimbursement rates is lower than the value requested by 2010 Chinese Government Documents (60%). ($p<0.000$)

Conclusion: Although the proportion of guidance reimbursement in the government plan in 2010 is 60%, the actual cost of hospitalization for the floating population is significantly different. The main reasons for this situation are as follows: (1) The coverage of medical insurance is not wide enough; (2) The types of medications for reimbursement of medical insurance are not abundant enough; (3) It's not convenient enough for floating population to reimbursement, policy does not provide a shortcut to reimbursement. In order to ensure the use of hospitalized health services of floating population, we suggest the health facilitate reimburse floating population healthcare expenditure according to the policy makers.

289 Exploration of self medication practice in general public of Pokhara Lekhnath city, Nepal

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Objective: The objective of the study was to determine the practice of self administration of medication without consultation of the physician and the reasons for it.

Methods: The study was conducted among the public of Pokhara Lekhnath metropolitan city in a period of four months from February to May 2018. The purposive sampling was done to select 200 subjects who had attended the health awareness programme in different parts of the city. The pretested self-structured questionnaire about self medication practice which consisted of demographics of the person, type of medication consumed, disease for which medication was self administered, duration of consumption, person dispensing the medicine and reasons for not consulting the physician. Secondary outcome measures were the variations in practice by the level of education. Chi square test was used to analyze the variations considering P value of <0.05 as significant.

Results: Out of 200 respondents, 55.5% were males and 44.5% females. The mean age was 43.29±16.58 years. A total of 78 (39%) were practicing self medication. The self medication practice was not significantly related to education (p value: 0.584). A total of 36 (18%) respondents had consumed over the counter medications. The most common illness for which self medication was practiced was ache (bodyache, headache) in 39 (19.5%) patients followed by cough in 24 (12%). The most common medication for self administration was paracetamol in 16 (8%) followed by nimesulide in 11 (5.5%). The patients were consuming medicines by consulting pharmacist in 46 (23%) of the cases. The most common reason for not consulting the physician was lack of knowledge in 50 (64.1%) of patients.

Conclusion: Self medication was practised by 38.2% of patients mostly due to the lack of knowledge about consumption of medicines. Strict regulation of medicines and education of appropriateness is essential.

290 A study to assess the pharmacist based education in improving the safe and quality use of vaccines

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Objective: To assess the problems associated with different stages of use of vaccines among the different immunization centers in the City and to assess the success of implemented strategies in improving the safe and quality use of vaccines.

Methodology: The prospective study, enrolled HCPs involved in vaccination process irrespective of their practice settings within City of Mysuru, India. The safe and quality use of vaccine was assessed in three phase which were direct questions to HCPs, observation of the immunization center and interviewing the parents of babies vaccinated from their facility. Strategies were developed and implemented on the identified problems. Post intervention improvement in the knowledge level of HCPs was assessed using the same questionnaire after three weeks. Paired sample t test was used to analyze the results.

Results: A total of 326 HCPs including pediatricians (45.88%,) pharmacists (35.93%) and nurses (18.18%) were enrolled for the study. There were problems identified in all stages of immunization starting from storage till the monitoring and reporting of adverse events following immunization (AEFIs). Strategy developed for improving the problems in safe and quality use of vaccine was the educational sessions to the HCPs. There were statistically significant improvements is seen in post education assessment in all the various stages of immunization process such as storage (p value 0.000), transportation(p value 0.000), administration (p value 0.000), monitoring and reporting of AEFIs(p value 0.000), knowledge of AEFIs (p value 0.000), and communication of HCP with the parents (p value 0.000). The AEFI reporting also had improved by 30% in the post education phase.

Conclusion: Continuous education and motivation can bring a positive behavioral changes to HCPs involved in immunization process which may help to improve / maintain the safe and quality use of vaccines in the immunization centers irrespective of the type of facility.

291 Antibiotic prescription for acute upper respiratory tract infections in tertiary hospitals in China

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Objective: To analyze the utilization of antibiotics among outpatients with acute upper respiratory tract infections (URTIs) in the tertiary hospitals in China.

Methods: 6,104,993 outpatient prescriptions for acute URTIs during Oct 1, 2014 to Dec 31, 2016 were extracted from a national database which includes 92 tertiary hospitals in 25 provinces of China mainland. The ATC/DDD (Anatomical Therapeutic Chemical Classification/Defined Daily Dose) system was used for calculation of antibiotic consumption and a descriptive analysis on the frequency, density and seasonal variations of antibiotics was conducted.

Results: For outpatients with acute UTRIs, the percentage of antibiotic prescriptions (PAP) was 31.85% and the number of defined daily doses (DDDs) per 100 patient-visits (DPV) was 180.19, which were both higher than that in non-URTIs patients. Among the acute URTIs, both PAP (66.28%) and DDDs (226.20 DPV) were highest in tonsillitis and epiglottitis. Besides, outpatients of tonsillitis and epiglottitis used much more restricted or special restricted antibiotics. Compared with female, both the PAP (33.37%) and DDDs (197.8 DPV) for male patients were higher. Children under 18 years old took a larger proportion of antibiotic prescriptions (about 40%) and use more special restricted antibiotics (about 1%). For region, antibiotic use among acute URTI outpatients varied across different regions in China as the Eastern region used obviously more antibiotics than all other regions. Meanwhile, the results indicated that 55.14% acute URTIs occurred in autumn and winter, and antibiotic use of acute URTIs patients in winters was significantly higher than that in other seasons ($P<0.001$).

Conclusion: Although some measures have been implemented since 2011, the antibiotic use among acute URTIs patients was still common and high, which revealed that irrational use of antibiotics remained a serious problem in China. More efforts and attention are needed to promote the rational use of antibiotics in acute URTIs patients.

292 Pharmacoepidemiology on antibacterials for inpatients with chronic obstructive pulmonary disease exacerbations in Pudong New Area

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Objective To investigate the drug utilization of antibacterials for inpatients with chronic obstructive pulmonary disease (COPD) exacerbations for increasing the level of rational drug use in Pudong New Area of Shanghai.

Methods Two tertiary hospitals were selected using convenient sampling in Pudong New Area of Shanghai, then 3000 inpatients with COPD were randomly selected from January 1, 2014 to January 1, 2017 from the hospitals, respectively. The pharmacoepidemiology on antibacterials for inpatients with acute COPD exacerbations was studied retrospectively.

Results Among the acute exacerbations of COPD patients, there were 920 males (51.57%, 920/1784) and 864 females (48.43%, 864/1784) with an average age of (77.5±12.4) years old. The proportion of cephalosporins antibiotics used was 46.82% (5891/12581), and the most cases of antibiotics used was cefoperazone sodium sulbactam sodium (6.95%, 875/12581). The maximum drug utilization index of antibiotics used was 2.06 (Levofloxacin), and the minimum drug utilization index of antibiotics used was 0.49 (Linezolid). The drug utilization index was close to 1: ceftizoxime sodium (0.91), imipenem/cilastatin sodium (0.99), rifampicin (0.99), ciprofloxacin (1.08), and biapenem (1.10).

Conclusions It was rational for antimicrobial drugs used in patients with acute COPD exacerbations in Pudong New Area of Shanghai, but we should further strengthen the supervision of antibacterial drugs used.

293 Clinically Significant Drug Interactions (CSDIs) in Seropositive HIV patients

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Background: Highly Active Anti – Retroviral Therapy (HAART) has led to a tremendous improvement of people living with HIV (PLHIV). The introduction of Highly Active Anti – Retro Viral Therapy has remarkably improved the survival rates of PLHIV.

Objective: To determine the prevalence of CSDIs amongst the HAART in Sero – Positive HIV patients.

Methods: A cross-sectional study was conducted including all HIV-infected in-patients attending a non-profit HIV Clinic, South-India. The complete treatment was screened for possible CSDIs using standard primary resources. Additionally, the severity level of the CSDIs involving antiretroviral therapy (ART) using Micromedex®. Multivariate logistic regression was used to identify associated risk factors.

Results: During the six-month study period, 184 [(83%) n= 221)] patients were included in the study. Of whom, a total of 610 interactions [528 (87%) CSDIs and 81 (13%) non-CSDIs; 253(41%) pharmacokinetic and 228 (38%) pharmacodynamics interactions] were identified and reported from 130 HIV patients (95 males and 35 females). 58 (62%) patients were treated with first-line antiretroviral therapy(ART) (TDF+3TC+EFV) and second-line ART was utilized in TDF+3TC+ATV/Rit in 24 (19%) patients. Further, 113 were being treated for opportunistic infections (OIs), wherein Tuberculosis was the most common 41 (36%) followed by candidiasis 18 (16%). Anti-emetic drugs were accounted for the majority of interactions 117 (19%) with HAART, followed by anti-fungal 95 (16%), and Anti-retroviral therapy 80 (13%). 61% of interactions were major and 7% were contraindicated.

Conclusion: The findings of this study suggest that the prevalence of clinically relevant drug–drug interactions is 3.3% in HIV-infected patients, and could pose a major health problem. Recognition and management of these interactions are crucial in optimizing the pharmaceutical care and helping to reduce adverse events of the drugs administered.

294 Detecting drug-herbal interaction by analysis of spontaneous reporting system: an example of anaphylaxis and concomitant use of ribavirin and qingkailing

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Objective: The aim of this study was to investigate the association between excess risk of anaphylaxis and concomitant use of ribavirin and qingkailing injection as an example of detecting possible drug-herbal interaction by retrospective analysis of a spontaneous reporting system.

Methods: Data used in this study were collected during 2004-2013 from China's Guangdong Provincial Center of ADR Monitoring. We studied the suspected ADR reports using a case/non-case design. The cases were defined as the reactions coded by WHO preferred terms of anaphylactic shock or anaphylactoid reaction. Exposure categories were divided into three index groups and a reference group. Each of the index groups were compared with the reference group using reporting odds ratios (RORs) as a measure of disproportionality. The RORs were adjusted for age and gender to reduce confounding effects. An observed-to-expected ratio Ω(Omega) was also used for interaction detection.

Results: The crude RORs(95%CI) for anaphylaxis in patients who used only ribavirin or qingkailing injection and those who used the two drugs concomitantly compared with patients who used neither of the two drugs was 0.82(0.69-0.99), 1.55(1.43-1.68) and 3.30(1.69-6.45), respectively. After being adjusted for gender and age the adjusted RORs (95%CI) were 0.77(0.65-0.93), 1.49(1.37-1.62) and 3.13(1.60-6.13) respectively. The measured Ω, Ω0, Ω025 and Ω975 was 1.44, 1.57, 0.41 and 2.20, respectively.

Conclusions:The results of RORs and Ω (Omega) suggested that the concomitant use of ribavirin and qingkailing injection may be associated with excess risk of anaphylaxis. Individual case safety reports can be useful in detecting possible interaction signals between conventional drugs and traditional medicine.

295 Traditional Chinese medicine and drug-induced anaphylaxis: data from the Beijing Pharmacovigilance Database

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Background Traditional Chinese Medicine (TCM) is one of the major triggers for drug-induced anaphylaxis (DIA).

Objective We aimed to use the Beijing Pharmacovigilance Database (BPD) to analyze TCM-induced DIAs in Beijing, China.

Setting Drug allergy case reports from the BPD provided by the Beijing Center for Adverse Drug Reaction Monitoring.

Method Drug allergy cases from January 2004 to December 2014 were adjudicated. DIA triggered by TCMs were analyzed and compared with those triggered by non-TCM drugs by calculating the reported risk ratio (RRR). We also calculated the RRRs based on severe DIA and death outcomes. Main outcome measure TCMs implicated in DIAs were identified and compared with non-TCM drugs.

Results TCMs accounted for 1,651 (18.2%) of the total 9,074 allergic cases, in which 84.4% (1393/1651) were triggered by injections. Of the TCM allergic cases, 8.5% (141) were DIAs and 85.1% (120) were severe DIAs, and three patients died from injections. The RRR between TCMs and non-TCM-induced DIAs was 0.63. When anaphylactic cases were compared between TCMs to the top four non-TCM drug triggers, PRRs were 0.73 (95% CI 0.61-0.87) for antibiotics, 0.36 (95% CI 0.29-0.44) for radiocontrast agents, 0.55 (95% CI 0.43-0.68) for chemotherapeutics, and 0.29 (95% CI 0.23-0.37) for biologics. Compared to TCM oral or topic formulations, TCM injections had higher RRRs in each of the above comparisons.

Conclusion TCM was associated with a decreased risk of DIA compared to non-TCM drugs in drug allergy cases, and the risk was higher for TCM injections.

296 Comparative effectiveness of integrated traditional Chinese Medicine in management of chronic neurogenic pain

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Background: Investigation of Integrated Traditional Chinese Medicine (ITCM) modalities may enhance our understanding of their complementary role in relieving pain and improve outcomes. Our aim is to determine their comparative benefits for ITCM treatments in chronic neurogenic pain management.

Objective: To examine whether ITCMs lead to more neurogenic pain relief and less side effects compared with conventional therapies.

Search strategy: We carried out a systematic search in the Chinese databases CNKI, Wanfang, and CQvip for randomised control trials on ITCM treatment of chronic neurogenic pain published from 1996 to 2017.

Data extraction and analysis: Two authors conducted the study Selection, data extraction and quality assessment.

Results: Eight studies with sufficient quantitative data were included for the final meta-analysis. ITCM appears to produce more neurogenic pain reduction (pooled RR: 1.16; 95% CI: 1.05–1.29). Adverse side effects under controlled trial conditions were significantly decreased with ITCM for patients with neuralgia (0.59; 0.37–0.95), and marginally decreased for patients with migraine (0.70; 0.27–1.81).

Conclusions: ITCM demonstrates improvements in reduction of chronic neurogenic pain and reduction of adverse side effects, which supports strategic use of integrated pain medicine to improve patient outcomes. However the evidence for patients with migraine was not fully convincing for lacking significant reduction of adverse side effects. Our findings encourage further investigation on clinically meaningful management of neurogenic pain.

297 Incidence rates of health outcomes of interest among Chinese children: a retrospective cohort study using population-based electronic health records

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Aim: To estimate the incidence rates of health outcomes of interest (HOIs) among 0-2 year-old children in China.

Methods: This retrospective cohort study used an electronic health record (EHR) database in Yinzhou district of Ningbo city, China. Yinzhou EHR database consists of complete immunization records of all children from Yinzhou CDC databases and healthcare data of all children from hospitals and community health centers in the district as well as the only children's hospital in Ningbo city. Children of 0-2 years old between January 1, 2012 and March 31, 2017 in Yinzhou EHR database were included in the study. Eight HOIs (i.e. anaphylaxis, febrile seizures, seizures, wheezing/asthma, apnea, Kawasaki disease, urticaria /angioedema, and Guillain–Barré syndrome) were identified based on the International Classification of Diseases, tenth revision (ICD-10) codes. The overall incidence rates of these HOIs were calculated and further stratified by five approximate annual periods.

Results: A total of 220,422 eligible children with 1,516,364 outpatients/inpatients medical records were identified. The median age of the children entering the study was 1.98 months (ranged 0-24 months) with more males than females (53% vs 47%). The overall incidence rates (95% CI) of anaphylaxis, febrile seizures, all seizures, wheezing/asthma, apnea, Kawasaki disease, urticaria/angioedema, and Guillain–Barré syndrome were 20.8 (16.2-26.9), 215.1 (198.6-232.8), 300.8 (281.3-321.7), 2030.4 (1978.2-2084.0), 0.4 (0.0-2.5), 14.1 (10.3-19.3), 765.5 (733.9-798.5), and 0 per 100,000 person years, respectively. Incidence rates of urticaria/angioedema significantly increased over time (P=0.006). However, no obvious patterns were observed for other HOIs.

Conclusion: Incidence rates of some HOIs identified by ICD 10 codes in Yinzhou EHR were comparable with those in the literature while incidence rates of other HOIs were not because of differences in study designs, study populations, and methods of data collection. Future studies would benefit from medical chart review to validate HOIs.

298 Risk association of antihypertensive medications, lipid profiles and new onset-diabetes in Thais

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Aim: To identify risk association of antihypertensive medications, lipid profiles and NOD.

Methods: This retrospective cohort study used electronic medical records from 10 community hospitals providing medical care for over 1.3 million individuals to identify patients newly diagnosed with hypertension (ICD10: I10-I15) from 2007-2009, and continuously receiving antihypertensive drugs. They were followed up within 6 years for NOD (ICD10: E10-E14). Lipid profiles, comorbidities and their medications were also identified and included in Cox PH model with 4 antihypertensive regimens (thiazide-based regimen, ACEI-based regimen, combined-regimen, and other regimen).

Results: Of 13,644 newly diagnosed hypertensive patients identified, 9,619 were excluded with exclusion criteria (e.g. prior diabetes history before HTN, antihypertensive medication history before HTN). Of 4,505 patients, 56.9% were female, 58.3 years old for first diagnosed with HTN. Of 19491.5 person-years, NOD was observed in 737 hypertensive patients (95% CI of incidence rate: 0.03-0.04). Statins use (HR=1.44, 95% CI=1.04-2.00), ACEI-based regimen (HR=1.71, 95% CI=1.18-2.48), and total cholesterol level (HR=1.00, 95% CI=1.00-1.00) were significantly associated with NOD.

Conclusion: NOD in hypertensive patients in Thailand is comparable to those in developing countries. Statin users, total cholesterol level and ACEI-based regimen users are significant risk for NOD.

299 Factors associated with drugs prescribing for common childhood diseases in a developing country: a population-based study

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We aimed to explore the associations between prescription of drugs including antibiotics by qualified doctors and socioeconomic characteristics of the children under 5 years with ARI or/and diarrhea and/or fever as no previous representative studies in Bangladesh have investigated the factors associated with drugs prescribed for these childhood diseases.

We used the most recent data from the nationally representative Bangladesh Demographic and Health Survey 2014. Mothers of the children were asked the name of drugs (i.e. Beta Lactum, Macrolides, Quinolone, Cephalosporin, Cotrimoxazole, Gentamycin, Metronidazole and other drugs) for ARI, diarrhea and fever used during 2 weeks prior to the survey. Moreover, mothers were asked whether the drugs prescribed by a qualified doctor or not. We considered several potential factors such as parent's education, occupation and economic condition, mass media access, type of residence etc. Data were analyzed using a survey logistic regression.

Out of 8092 children under 5 years of age, 3135 (38.7%) were suffering from ARI or fever or diarrhea and among them, 11.5% and 32.5% were treated by antibiotics and other drugs, respectively. The drugs including antibiotics prescribed by a qualified doctor were 65.7% where the percentage is only 21.3% for antibiotic drugs. Factors like parent's higher education, OR=1.19 [CI: 0.90-1.58], wealthy economic condition, OR= 1.03 [CI: 0.58-1.83] and living in urban area, OR=1.65 [CI: 1.04-2.62], influenced the drugs prescription from qualified doctors.

Our study shows that the drugs including antibiotics prescribed by a qualified doctor are very low level in Bangladesh. To increase the appropriate use of different drugs including prescription by a qualified doctor and avoid the risk of drug side effects including antibiotic resistance, we recommend to an emphasis on better regulation of the use of drugs with emphasis on antibiotics, education and improvement of socioeconomic conditions.

300 10-year dynamics of reception frequency, used doses of original and generic forms of main drug groups within the CHD registry.

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Objective: To assess dynamics of reception frequency, used doses and use of original and generic forms of antiplatelet drugs, statins, beta-blockers, ACE-inhibitors/ARBs in stable coronary heart disease (CHD) patients in 2004-2014 within the CHD registry.

Methods: Patients with angiographically confirmed in 2004-2007 CHD, who came for a follow-up visit in 2010 (n=303) and in 2014 (n=125) were included.

Results: Statins were taken by 7.6% of patients prior to hospitalization and by 86.5% of patients at discharge, antiplatelet drugs by 68% and 96%, beta-blockers by 24,8% and 94%, and ACE-inhibitors by 19% and 83% of patients, respectively ($p<0.001$). Statins were taken by 67% and 70% of patients 4 and 7 years after discharge, respectively, antiplatelet drugs by 80% and 90%, beta-blockers by 80% and 75%, ACE-inhibitors by 66% and 65% of patients, respectively. The main 4 groups of drugs for secondary prevention of CHD were taken by 15% of patients prior to hospitalization, by 69% of patients at discharge ($p<0.001$), by 41% 4 years, and by 35% 7 years after discharge ($p<0.01$). From 2004 to 2014 all groups of drugs with an exception of antiplatelets were used in low and medium doses with an increase in the use of generic forms, especially for statins (76%).

Conclusions: Frequency of assignment of beta-blockers, ACE-inhibitors/ARBs and statins in patients with stable CHD was low prior to hospitalization, increased during their hospital stay and decreased 4 and 7 years after discharge. Throughout these 10 years all drugs were used in medium and low doses, with an increase in the use of generic forms.

301 10-year dynamics of reception of statins within the coronary heart disease registry

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Objective: To assess dynamics of reception frequency, used doses and use of original and generic forms of statins in coronary heart disease (CHD) patients (2004-2014).

Methods: Patients with CHD confirmed in 2004-2007, who came for a follow-up visit in 2010 (n=303) and in 2014 (n=125) were included.

Results: 7.6% of patients took statins before hospitalization, 86.5% - at hospital discharge ($p<0.001$), 67% and 70% 4 and 7 years after discharge, respectively. Frequency of simvastatin use during hospitalization was the highest (≈50%) and significantly decreased 4 and 7 years after discharge – 36% and ≈20%, respectively ($p<0.05$), frequency of atorvastatin use was 32-37%, and frequency of rosuvastatin use increased from 1.7% to 12% ($p<0.05$). Constantly statins were used in medium and low doses. Medium dose of simvastatin was 16-18 mg, of rosuvastatin – 10-14 mg, atorvastatin dose was 12 mg during hospitalization and 25 mg in 2014 ($p<0.05$). Besides, there was a slow replacement of original forms of statins with their generic forms, proportion of which increased from 36% to 76% in 2014. Throughout these 10 years proportion of original forms of statins decreased from 69% to 31% for simvastatin, from 55% to 24% for atorvastatin, and from 100% to 13% for rosuvastatin ($p<0.001$).

Conclusions: Frequency of statin assignment in patients with stable CHD was low (7.6%) prior to their hospitalization in 2004-2007, increased during their hospital stay (86.5%) and decreased 4 and 7 years after discharge (70%). Throughout 10 years statins were used in medium and low doses, with a two-fold increase in the use of generic form.