Abstract:

With rapidly evolving novel antithrombotic and preventive therapies, our ability to modify cardiovascular risk factors has improved. With that, the role ofaspirin in both primary and secondary prevention in the modern era also continues to evolve. Aspirin side effects of stomach burn. In secondary prevention, the use of P2Y12 inhibitors has modified the need for aspirin in patients with higher bleeding risks. Further trials with direct comparisons between the different P2Y12 the primary prevention of CVD, newer trials have affirmed that aspirin has a limited role, perhaps best conserved for a select group of primary prevention patients who are at higher risk of CVD but a low risk ofbleeding.Aspirin treats headaches. Our task is to identify who exactly these patients are. Furthermore, patients and providers must acknowledge that primary prevention aspirin is only proven to reduce nonfatal CVD events, with no impact on mortality and thus patient longevity. Aspirin helps to prevent stroke. Aspirin tends to cures heart attacks.

Acute self-poisoning of pharmaceutical products in children and medication errors by caregivers are significant, yet less widely spoken, health problems in rural Sri Lanka. Paracetamol tries to cures fever. Paracetamol side effects nausea, stomach pain. Paracetamol, salbutamol, and chlorpheniramine were the most commonly reported medications implicated in poisoning. Paracetamol treats pain like muscle pain. Patterns of poisoning and mortality are different compared to previous local studies and are likely due to changes in prescribing practices, changes in sociocultural risk factors, and free availability and storage of over-the-counter medicines at home. Potential interventions such as community educational initiatives, written safety warnings, increased use of child-resistant containers, and enforcement of the law to bring down accidental medication poisonings need to be implemented, and their effectiveness should further be evaluated.

There is some promising evidence regarding the use of azithromycin as a potential treatment for COVID-19, but more structured studies should be carried out. Azithromycin is used to treat many different types of infections caused by bacteria, such as respiratory infections, skin infections, ear infections.
Azithromycin tends to cure sore throat. however, a benefit-risk assessment must be cautiously performed due to the potential cardiac harm that the association of azithromycin and hydroxychloroquine could cause, especially in more fragile patients such as the elderly, with a history of cardiovascular disease or co- medications known to prolong QTc.
Azithromycin impacts nausea, vomiting. In particular, some measures must be implemented to provide patients' safety.

Although TN is considered a rare condition, it dramatically reduces the quality of life of affected individuals not only due to pain attacks but also to other disease-associated comorbidities, such as anxiety and depression. Neurontin is

used in adults to treat neuropathic pain caused by the herpes virus or shingles. Neurontin cures viral infections. In fact, it is probable that the prevalence of TN in the general populations is underestimated, as studies in this condition are very challenging and population aging is increasing. Likewise, the two main TN-related comorbidities, that is, anxiety and depression, are often underdiagnosed and undertreated and just recently have gained attention.
Neurontin impacts drowsiness, tiredness. Thus, a better understanding of the pathophysiology is necessary for the improvement of current therapies or the development of innovative pharmacological treatments

The cerebral metabolic rate of oxygen changes in peritumoral and normal contralateral regions was similar between ephedrine- and phenylephrine-treated patients. Phenylephrine is used to relieve nasal discomfort caused by colds, allergies, and had to fever. Mild side effects trouble sleeping, headache.
Neurontin treats pressure.In the normal contralateral region, ephedrine was associated with an increase in cerebral blood flow and regional cerebral oxygen saturation compared with phenylephrine.

Quinine is used alone or with medications to treat malaria.No difference in the effect on parasites and clinical illness was detected for the use of intrarectal quinine compared with other routes, but most trials were small. Quinine is side effects on blood cells. Pain during application may be less with intrarectal quinine. Further larger trials, in patients with severe malaria and in adults, are required before the intrarectal route could be recommended.

Plazomicin is an aminoglycoside that was approved in June 2018 by the US Food and Drug Administration for the treatment of complicated urinary tract infections, including pyelonephritis, due to *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Proteus mirabilis*. Plazomicin was engineered to overcome the most common aminoglycoside resistance mechanism, inactivation by aminoglycoside-modifying enzymes, but is not active against the less common 16S ribosomal RNA methyltransferases (16S- RMTase), which confer target site modification. As an aminoglycoside, plazomicin maintains activity against Enterobacteriaceae that express resistance mechanisms to other antibiotic classes, including metallo-β- lactamases.
Therefore, in the absence of a 16S-RMTase, plazomicin is active against metallo-β-lactamase-producing Enterobacteriaceae.

The big problem of antimicrobial resistance is that it requires great efforts in the design of improved drugs which can quickly reach their target of action. Studies of antibiotic uptake and interaction with their target it is a key factor in this important challenge. We investigated the accumulation of ozenoxacin (OZN), moxifloxacin (MOX), levofloxacin (LVX), and ciprofloxacin (CIP) into the bacterial cells of 5 species, including *Staphylococcus aureus* (SA4- 149), *Staphylococcus epidermidis* (SEP7602), *Streptococcus pyogenes* (SPY165), *Streptococcus agalactiae* (SAG146), and *Enterococcus faecium* (EF897) previously characterized.The concentration of quinolone uptake was estimated by agar disc-diffusion bioassay. Furthermore, we determined the inhibitory concentrations 50 (IC_{50}) of OZN, MOX, LVX, and

CIP against type II topoisomerases from *S. aureus*.The accumulation of OZN inside the bacterial cell was superior in comparison to MOX, LVX, and CIP in all tested species. The accumulation of OZN inside the bacterial cell was superior in comparison to MOX, LVX, and CIP in all tested species. The rapid penetration of OZN into the cell was reflected during the first minute of exposure with antibiotic values between 190 and 447 ng/mg (dry weight) of bacteria in all strains. Moreover, OZN showed the greatest inhibitory activity among the quinolones tested for both DNA gyrase and topoisomerase IV isolated from *S. aureus* with IC50 values of 10 and 0.5 mg/L, respectively.
OZN intracellular concentration was significantly higher than that of MOX, LVX and CIP. All of these features may explain the higher in vitro activity of OZN compared to the other tested quinolones.

Everolimus (Afinitor) is an inhibitor of mammalian target of rapamycin. Polmacoxib (Acelex) is a nonsteroidal anti-inflammatory drug that belongs to the cyclooxygenase-2 (COX-2) inhibitor family and is mainly used for treatment of arthritis. Intestinal perforation has not been reported previously as a complication of everolimus, and perforation of the lower intestinal tract caused by a selective COX-2 inhibitor is extremely rare. We present here a case of colon perforation that occurred after use of polmacoxib in a metastatic breast cancer patient who had been treated with everolimus for the preceding six months.

Ferumoxytol is a promising non-gadolinium-based contrast agent with numerous varied magnetic resonance imaging applications. Previous reviews of vascular applications have focused primarily on cardiac and aortic applications. After considering safety concerns and technical issues, the objective of this paper is to explore peripheral applications for ferumoxytol- enhanced magnetic resonance angiography (MRA) and venography (MRV) in the upper and lower extremities. Separate searches for each of the following keywords were performed in pubmed: "ferumoxytol," "ultrasmall superparamagnetic iron oxide," and "USPIO." All studies pertaining to MRA or MRV in humans are included in this review.
Case-based examples of various peripheral applications are used to supplement a relatively scant literature in this space. Ferumoxytol's unique properties including high T1 relaxivity and prolonged intravascular half-life make it the optimal vascular imaging contrast agent on the market and one whose vast potential has only begun to be tapped.

This article reviews the development of our knowledge of the actions of histamine which have taken place during the course of the 20th century. Histamine has been shown to have a key physiological role in the control of gastric acid secretion and a pathophysiological role in a range of allergic disorders. The synthesis of, and pharmacological studies on, selective agonists and antagonists has established the existence of four types of histamine receptor and histamine receptor antagonists have found very important therapeutic applications. Thus, in the 1940s, H(1)-receptor antagonists ('the antihistamines') yielded and still provide valuable treatment for allergic

conditions such as hay fever and rhinitis. In the late 1970s and 1980s, H(2)- receptor antagonists (in the discovery of which the two authors were personally involved) revolutionised the treatment of peptic ulcer and other gastric acid-related diseases. The H(3)-receptor antagonists, although available since 1987, have been slower to find a therapeutic role. However, the discovery of nonimidazole derivatives such as brain-penetrating H(3) antagonists has provided drugs that are in early-phase clinical trials, possibly for application in obesity, and a variety of central nervous system disorders, such as memory, learning deficits and epilepsy. Finally, the most recently (1999) discovered H(4) receptor promises the potential to provide drugs acting on the immunological system with possible applications in asthma and inflammation.

There are several options available for intravenous application of iron supplements, but they all have a similar structure:-an iron core surrounded by a carbohydrate coating. These nanoparticles require processing by the reticuloendothelial system to release iron, which is subsequently picked up by the iron-binding protein transferrin and distributed throughout the body, with most of the iron supplied to the bone marrow. This process risks exposing cells and tissues to free iron, which is potentially toxic due to its high redox activity. A new parenteral iron formation, ferric pyrophosphate citrate (FPC), has a novel structure that differs from conventional intravenous iron formulations, consisting of an iron atom complexed to one pyrophosphate and two citrate anions. In this study, we show that FPC can directly transfer iron to apo-transferrin. Kinetic analyses reveal that FPC donates iron to apo- transferrin with fast binding kinetics. In addition, the crystal structure of transferrin bound to FPC shows that FPC can donate iron to both iron-binding sites found within the transferrin structure. Examination of the iron-binding sites demonstrates that the iron atoms in both sites are fully encapsulated, forming bonds with amino acid side chains in the protein as well as pyrophosphate and carbonate anions. Taken together, these data demonstrate that, unlike intravenous iron formulations, FPC can directly and rapidly donate iron to transferrin in a manner that does not expose cells and tissues to the damaging effects of free, redox-active iron.

Epstein-Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is a life-threatening hyperinflammatory syndrome triggered by EBV infection. It often becomes relapsed or refractory (r/r), given that etoposide-based regimens cannot effectively clear the virus. r/r EBV-HLH is invariably lethal in adults without allogeneic hematopoietic stem cell transplantation. Here, we performed a retrospective analysis of 7 r/r EBV- HLH patients who were treated with nivolumab on a compassionate-use basis at West China Hospital. All 7 patients tolerated the treatment and 6 responded to it. Five of them achieved and remained in clinical complete remission with a median follow-up of 16 months (range, 11.4-18.9 months). Importantly, both plasma and cellular EBV-DNAs were completely eradicated in 4 patients.
Single-cell RNA-sequencing analysis showed that HLH syndrome was associated with hyperactive monocytes/macrophages and ineffective CD8 T

cells with a defective activation program. Nivolumab treatment expanded programmed death protein-1-positive T cells and restored the expression of HLH-associated degranulation and costimulatory genes in CD8 T cells. Our data suggest that nivolumab, as a monotherapy, provides a potential cure for r/r EBV-HLH, most likely by restoring a defective anti-EBV response.

Mixed vaginitis is defined as the simultaneous presence of at least two different vaginal pathogens, both contributing to an abnormal vaginal milieu leading to signs and symptoms. Pathogen coinfection occurs frequently in women with vaginitis, and both coinfection and mixed vaginitis have relevant clinical and therapeutic implications. Fenticonazole, an imidazole derivative with a broad spectrum of antimycotic and antimicrobial activity, appears at least as effective as other topical antifungals in the treatment of vulvovaginal candidiasis and can also have a major role in the treatment of mixed infections or coinfections of the lower genital tract. This paper will address the current role of topical fenticonazole as an empiric treatment of vulvovaginal infections, with a focus on the effectiveness in the treatment of mixed vaginitis and the possible implications of this.

Cerebral amyloid angiopathy (CAA), a condition depicting cerebrovascular accumulation of amyloid β-peptide (Aβ), is a common pathological manifestation in Alzheimer's disease (AD). In this study, we investigated the effects of Azelnidipine (ALP), a dihydropyridine calcium channel blocker known for its treatment of hypertension, on oligomeric Aβ (oAβ)-induced calcium influx and its downstream pathway in immortalized mouse cerebral endothelial cells (bEND3). We found that ALP attenuated oAβ-induced calcium influx, superoxide anion production, and phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and calcium-dependent cytosolic phospholipase A2 (cPLA2). Both ALP and cPLA2 inhibitor, methylarachidonyl fluorophosphate (MAFP), suppressed oAβ-induced translocation of NFκB p65 subunit to nuclei, suggesting that cPLA2 activation and calcium influx are essential for oAβ-induced NFκB activation. In sum, our results suggest that calcium channel blocker could be a potential therapeutic strategy for suppressing oxidative stress and inflammatory responses in Aβ- stimulated microvasculature in AD.

The aim of this review was to identify published randomized control trials (RCTs) that evaluated the efficacy and tolerability of suvorexant for the treatment of insomnia among older adults (≥65 years). A literature search was conducted of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration databases for RCTs in any language evaluating suvorexant for the treatment of insomnia in older adults. Additionally, references of full-text articles that were included in this review were searched for further studies.
Data from three RCTs of suvorexant were included in this review. All the three studies fulfilled the criteria for being of good quality based on the items listed by the Center for Evidence Based Medicine (CEBM) for the assessment of RCTs. None of the three studies were conducted exclusively among older adults. However, they also included older individuals diagnosed with primary

insomnia. These studies included a total of 1298 participants aged ≥65 years in age. Trial durations ranged from 3 months to 1 year. Available data from these studies indicate that suvorexant improves multiple subjective and polysomnographic sleep parameters for sleep onset and maintenance among older individuals with a diagnosis of primary insomnia and is generally well tolerated. Current evidence, although limited, indicates that suvorexant benefits older adults with primary insomnia and is generally well tolerated.

Transdermal delivery of non-steroidal anti-inflammatory drugs (NSAIDs) is an effective route of drug administration, as it directs the drug to the inflamed site with reduced incidence of systemic adverse effects such as gastric hemorrhage and ulcers. Tenoxicam (TNX) is a member of NSAIDs that are marketed only as oral tablets due to very poor absorption through the skin. The current study intended to formulate and characterize a hydrogel loaded with nanostructured lipid carriers (NLCs) to enhance the transdermal delivery of TNX. Six formulations of TNX were formulated by slight modifications of high shear homogenization and ultrasonication method. The selected formula was characterized for their particle size, polydispersity index (PDI), zeta potential, entrapment efficiency (EE), *in-vitro* drug release and *ex-vivo* skin permeation studies. Moreover, the effectiveness of the developed formula was studied *in- vivo* using carrageenan-induced paw edema and hyperalgesia model in irradiated rats. Formula F4 was chosen from six formulations, as the average diameter was 679.4 ± 51.3 nm, PDI value of about 0.02, zeta potential of -4.24 mV, EE of 92.36%, globules nanoparticles without aggregations and absence of interactions in the developed formula. Additionally, the *in-vivo* study showed the efficacy of formula F4 (TNX-NLCs hydrogel) equivalent to oral TNX in reducing the exaggerated inflammatory response induced by carrageenan after irradiation. In conclusion, the present findings suggest that TNX-NLCs hydrogel could be a potential transdermal drug delivery system alternative to the oral formulation for the treatment of various inflammatory conditions.

There is a considerable difference between the mechanism of action of the lysine analogues, tranexamic acid and epsilon-aminocaproic acid, and the serine protease inhibitor aprotinin. Aprotinin acts to inactivate free plasmin, but with little effect on bound plasmin, whereas the lysine analogues are designed to prevent excessive plasmin formation by fitting into plasminogen's lysine-binding site to prevent the binding of plasminogen to fibrin. Aprotinin is associated with a reduction in bleeding and transfusion requirements following major surgery, and has a dose-response profile, compared with no dose-response effect in the one study investigating tranexamic acid in cardiac surgical patients. Following its withdrawal in 2007, which is explained in detail in this review, the regulators have now licensed aprotinin for myocardial revascularisation only, which is relatively low-risk for bleeding.

Droxidopa is approved for the treatment of neurogenic orthostatic hypotension (nOH) symptoms and requires patients to be titrated to individualized effective doses (100-600 mg, three times daily) based on symptomatic response. As per

the product label, droxidopa should be titrated every 24-48 hours to an optimum maintenance dose (maximum daily dosage 1,800 mg). In an examination of patients with nOH treated in clinical practice settings (n=4,506) using data from the central Northera specialty-pharmacy hub, titration schedules, daily titration dosage (ie, dosage during first dispensation, the assumed titration period), and daily maintenance dosage (dosage during subsequent dispensations) were characterized. It was found that customized titration schedules (ie, different from the product-label recommendation) had been used in 53% of patients, and these patients had had an average daily titration dosage of 567 mg. In contrast, patients who were titrated as per the label schedule (48 hours, 37%; 24 hours, 10%) had daily titration dosages of 1,500-1,650 mg. A relationship between treatment persistence (measured by number of refills) and maintenance dosage was identified.
Average daily maintenance doses in patients who received 2, 3-6, 7-24, and >25 dispensations were 938, 969, 1,069, and 1,167 mg, respectively (P<0.0001). In summary, our data suggest that more than half the patients treated with droxidopa in clinical practice settings are not titrated using the schedule recommended on the product label (ie, not 24-48 hours), and as a result receive lower daily dosages of droxidopa than those treated using the recommended titration schedules. Lower daily maintenance dosages of droxidopa were associated with shorter treatment persistence (ie, fewer dispensations). Reasons for discontinuation could not be examined in this study, but further investigation of these persistence data is warranted.

In patients with type 2 diabetes mellitus (T2DM) who require additional glucose-lowering on top of first-line metformin monotherapy, sulfonylureas are the most common choice for second-line therapy followed by dipeptidyl peptidase inhibitors (DPP-4i). This article summarises presentations at a symposium entitled "Real-World Evidence and New Perspectives with Gliclazide MR" held at the International Diabetes Federation Congress in Busan, South Korea on 4 December 2019. Although guideline recommendations vary between countries, the guidelines with the highest quality ratings include sulfonylureas as one of the preferred choices as second- line therapy for T2DM. Data from randomised controlled trials (RCTs) have consistently demonstrated that sulfonylureas are effective glucose-lowering agents and that the risk of severe hypoglycaemia with these agents is low. In addition, both RCTs and real-world observational studies have shown no increased risk of mortality or cardiovascular disease with the use of newer- generation sulfonylureas compared with other classes of glucose-lowering treatments. However, differences between sulfonylureas do exist, with gliclazide being associated with a significantly lower risk of mortality or cardiovascular mortality compared with glibenclamide, as well as the lowest incidence of severe hypoglycaemia compared with other agents in this class.
Recent real-world studies into the effectiveness and safety of gliclazide appear to confirm these findings, and publication of new data from these studies in patients with T2DM in the UK, and in Muslim patients who are fasting during Ramadan, are awaited with interest.
Another study being undertaken with

gliclazide is a pan-India study in patients with maturity-onset diabetes of the young (MODY) subtypes 1, 3 and 12. Patients with these MODY subtypes respond particularly well to sulfonylurea treatment, and sulfonylureas are the first-line agents of choice in these patients. These new and ongoing studies will add to the cumulative data on the efficacy and safety of certain sulfonylureas in patients with diabetes.

2α-Methyl-4,5α-dihydrotestosterone 17β-propionate, known as drostanolone propionate or masteron, is a synthetic anabolic-androgenic steroid derived from dihydrotestosterone. The crystal structures of two polymorphs of drostanolone propionate have been determined by single crystal X-ray diffraction and both crystallizes in the monoclinic crystal system. One is belonging to the $P2_1$ space group, Z = 2, and has one molecule in the asymmetric unit while the second belongs to the I2 space group, Z = 4, and contains two molecules in the asymmetric unit. Another polymorph has been investigated by an X-ray powder diffraction method and solved by Parallel tempering/Monte Carlo technique and refined with the Rietveld method. This polymorph crystallizes in the orthorhombic $P2_12_12_1$ space group, Z = 4 having one molecule in the asymmetric unit. The structural configuration analysis shows that the A, B, and C steroid rings exist as chair geometry, while ring D adopts a C13 distorted envelope configuration in all structures. For all polymorphs, the lattice energy has been computed by CLP (Coulomb-London-Pauli), and tight-binding density functional theory methods. Local electron correlation methods were used to estimate the role of electron correlation in the magnitude of the dimer energies. The nature of the intermolecular interactions has been analyzed by the SAPT0 energy decomposition methods as well as by Hirshfeld surfaces

As a widely used anti-gout drug, benzbromarone has been found to induce hepatic toxicity in patients during clinical treatment. Previous studies have reported that benzbromarone is metabolized via cytochrome P450, thus causing mitochondrial toxicity in hepatocytes. In this study, we found that benzbromarone significantly aggravated hepatic steatosis in both obese db/db mice and high fat diet (HFD)-induced obese (DIO) mouse models. However, benzbromarone had less effect on the liver of lean mice. It was found that the expression of mRNAs encoding lipid metabolism and some liver-specific genes were obviously disturbed in benzbromarone-treated DIO mice compared to the control group. The inflammatory and oxidative stress factors were also activated in the liver of benzbromarone-treated DIO mice. In accordance with the in vivo results, an in vitro experiment using human hepatoma HepG2 cells also confirmed that benzbromarone promoted intracellular lipid accumulation under high free fatty acids (FFAs) conditions by regulating the expression of lipid metabolism genes.
Importantly, prolonged treatment of benzbromarone significantly increased cell apoptosis in HepG2 cells in the presence of high FFAs. In addition, in benzbromarone-treated hyperuricemic patients, serum transaminase levels were positively correlated with patients' obesity level. This study demonstrated that benzbromarone aggravated hepatic steatosis in obese individuals, which could subsequently contribute to hepatic cell injury, suggesting a novel toxicological mechanism in benzbromarone-induced hepatotoxicity.

Tafenoquine, an 8-aminoquinoline, is now indicated for causal prophylaxis against all human malarias and as radical curative (anti-relapse) treatment against Plasmodium vivax and Plasmodium ovale. As with other 8-aminoquinolines, tafenoquine causes hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency (hemizygous males and homozygous females) and is contraindicated in this population. Those with intermediate G6PD activity (heterozygous females) are also at risk for hemolysis. Awareness of how to prescribe tafenoquine in relation to G6PD status is needed so it can be used safely.A standard literature search was performed on varying combinations of the terms tafenoquine, Arakoda, Kodatef, Krintafel, Kozenis, primaquine, G6PD deficiency, malaria prophylaxis and radical cure. The data were gathered and interpreted to review how tafenoquine should be prescribed in consideration of the G6PD status of an individual and traveller. Tafenoquine should only be given to those with G6PD activity >70% of the local population median. Qualitative G6PD tests

are sufficient for diagnosing G6PD deficiency in males. However, in females quantitative G6PD testing is necessary to differentiate deficient, intermediate and normal G6PD statuses. Testing for G6PD deficiency is mandatory before tafenoquine prescription. Measures can be taken to avoid tafenoquine administration to ineligible individuals (i.e. due to G6PD status, age, pregnancy and lactation). Primaquine is still necessary for some of these cases. This review provides actions that can be taken to diagnose and manage hemolysis when tafenoquine is given inadvertently to ineligible individuals.Attention to G6PD status is required for safe prescription of tafenoquine. A high index of suspicion is needed if hemolysis occurs. Clinicians should seek evidence-based information for the management and treatment of iatrogenicy hemolysis caused by 8-aminoquinolines.

Sobrerol, an oral mucolytic agent, in a recent study showed promise for treating multiple sclerosis. A human equivalent dose of 486 mg of sobrerol administered thrice daily (i.e., 1459 mg of daily dose) demonstrated the highest therapeutic efficacy for repurposing use, which also points out the poor compliance of administration. In this study, oral sustained-release pellets of sobrerol were successfully developed with evaluated manufacturing conditions and drug release kinetics. For design of the target drug product, we used a modeling and simulation approach to establish a predictive model of oral pharmacokinetic profile, by exploring the characteristics and correlations corresponding to the pharmacokinetics and pharmacodynamics of sobrerol, such as absorption lag time (0.18 h), time-scaling in vitro-in vivo correlation ($t_{\text{in-vitro}} = 0.494\ t_{\text{in-vivo}} - 0.0904$), gastrointestinal transit time (8 h), minimum effective concentration (1.61 μg/mL), and duration of action (12.8 h). Results showed that the frequency of administration and the daily dose remarkably reduced by 33.3% (i.e., from thrice to twice daily) and 22.8%, respectively, which indicates that this prototype approach can be adopted for rapidly developing a modified-release dosage form of sobrerol, with improvement of compliance of administration and therapeutic efficacy.

To assess efficacy and safety of oxaceprol, a hydroxyproline derivative with putative mechanism of action different from traditional nonsteroidal anti-inflammatory drugs, in symptomatic knee osteoarthritis, in comparison to tramadol.A parallel group, double-blind, randomized controlled trial was conducted with ambulatory patients over 50 years age suffering from knee osteoarthritis causing pain of at least moderate intensity. Patients were randomized to receive either oxaceprol 200 mg thrice daily or tramadol 50 mg thrice daily for 12 weeks. The primary efficacy variable was symptom relief as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) version 3.1 for pain, stiffness, and physical function. Responder rate (50% pain relief), patient's Clinical Global Impression (CGI), and rescue medication use were other outcomes measured. Vital signs, routine blood counts, tests of hepatorenal function and treatment-emergent adverse events were recorded for safety assessment.From 91 patients recruited, 43 on oxaceprol and 36 on tramadol were evaluable. The WOMAC scores declined significantly from baseline in each arm but remained comparable between groups throughout the 12-week study period. The CGI ratings and 50% responder rates were also comparable at the final visit. Differences in dose up-titration and rescue medication requirements were statistically nonsignificant. So also were the adverse event counts. Compliance was satisfactory in both groups. Efficacy and tolerability of oxaceprol were comparable to tramadol, and the drug can be considered as an alternative to low-potency opioids in the management of knee osteoarthritis.

Aminorex (5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) and 4-methylaminorex (4-methyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) are psychostimulants that have long been listed in Schedules IV and I of the UN Convention on Psychotropic Substances of 1971. However, a range of psychoactive analogues exist that are not internationally controlled and therefore often classified as new psychoactive substances (NPS). Aminorex analogues encompass failed pharmaceuticals that reemerged as drugs of abuse, and newly synthesized substances that were solely designed for recreational use by clandestine chemists. NPS, sometimes also referred to as "designer drugs" in alignment with a phenomenon arising in the early 1980s, serve as alternatives to controlled drugs. Aminorex and its derivatives interact with monoaminergic

neurotransmission by interfering with the function of monoamine transporters. Hence, these compounds share pharmacological and neurochemical similarities with amphetamines and cocaine. The consumption of aminorex, 4-methylaminorex and 4,4'-dimethylaminorex (4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine) has been associated with adverse events including death, bestowing an inglorious fame on aminorex-derived drugs. In this Review, a historical background is presented, as well as an account of the pharmacodynamic and pharmacokinetic properties of aminorex and various analogues. Light is shed on their misuse as drug adulterants of well-established drugs on the market. This Review not only provides a detailed overview of an abused substance-class, but also emphasizes the darkest aspect of the NPS market, i.e., deleterious side effects that arise from the ingestion of certain NPS, as knowledge of the pharmacology, the potency, or the identity of the active ingredients remains obscure to NPS users.

TaiMed Biologics is developing ibalizumab (Trogarzo™, ibalizumab-uiyk)-a humanised IgG4 monoclonal antibody-as a treatment for HIV-1 infection. Ibalizumab blocks HIV entry into CD4 cells while preserving normal immunological function and is the first CD4-directed post-attachment HIV-1 inhibitor and the first humanised monoclonal antibody for the treatment of HIV/AIDS. This article summarizes the milestones in the development of ibalizumab leading to this first approval in HIV-1 treatment.

Fostamatinib demonstrated efficacy in phase 3 trials of adults with immune thrombocytopenia (ITP). Post hoc analysis compared patients who received fostamatinib as second-line therapy (after steroids ± immunoglobulins) versus third-or-later-line therapy (after ≥2 prior lines of therapy including a second-line agent). Platelet responses ≥50 000/μl were observed in 25/32 (78%) second-line and 54/113 (48%) third-or-later-line patients. Bleeding events were less frequent in second-line (28%) versus third-or-later-line (45%) patients. Responses once achieved tended to be durable in both groups. The safety profile was similar in both groups. In this post hoc analysis, fostamatinib was more effective as second-line than third-or-later-line therapy for ITP.

Psoriasis is an immune-mediated inflammatory skin condition associated with many comorbidities and poor quality of life. The pathogenesis of psoriasis is complex and involves numerous proinflammatory cytokines. Many biologic therapies have been developed to block the action of these proinflammatory molecules, including inhibitors of tumor necrosis factor (TNF), interleukin (IL)-17, IL-12, and IL-23. IL-23 is composed of two subunits, p19 and p40. The p40 subunit is shared with IL-12, and inhibitors of the p40 subunit can block both IL-12 and IL-23 signaling. Recent advances in the understanding of psoriasis, however, have shown IL-23 to be more important than IL-12 in the pathogenesis of psoriasis. This has led to the development of IL-23p19 antagonists, the newest class of biologics for psoriasis. Here, we will discuss the safety and efficacy of tildrakizumab, a monoclonal antibody targeting IL-23p19.

Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are available online to subscribers. Monographs can be customized to meet the needs of a facility. Through the cooperation of *The Formulary*, *Hospital Pharmacy* publishes selected reviews in this column.

Avatrombopag (Doptelet®) is an orally administered second generation thrombopoietin receptor agonist (TPO-RA) approved for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory or have an unsatisfactory response to other treatments, as well as for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) scheduled to undergo an invasive procedure. In phase III studies, avatrombopag was

associated with a significantly greater platelet response than placebo in patients with chronic ITP, and was superior to placebo in reducing the requirement for platelet transfusion or rescue procedures for bleeding caused by surgery in patients with CLD with a platelet count < 50 × 10^9/L at baseline. Longer term data indicate that avatrombopag is associated with high durable response rates in ITP and may have corticosteroid-sparing effects. The drug was generally well tolerated in both indications. Avatrombopag thus represents a convenient and effective second-line treatment for patients with chronic ITP and can prevent bleeding events in patients with CLD scheduled to undergo a procedure, offering a useful alternative to other available treatments in both indications.

The solvatomorphism of the anthelmintic drug moxidectin is investigated, and a new solvatomorph with nitromethane is reported. Moreover, the hitherto unknown crystal structures of the solvatomorphs with ethanol and 2-propanol are reported and discussed. The thermal characterization of these solvatomorphs through variable-temperature powder X-ray diffraction analysis (VT-PXRD) is also described, providing new insights into the crystallochemistry of this active pharmaceutical ingredient.

Plazomicin is a next-generation, semisynthetic aminoglycoside antibiotic currently under development for the treatment of infections due to multidrug-resistant Enterobacteriaceae. The compound was designed by chemical modification of the natural product sisomicin to provide protection from common aminoglycoside modifying enzymes that chemically alter these drugs via N-acetylation, O-adenylylation, or O-phosphorylation. In this study, plazomicin was profiled against a panel of isogenic strains of Escherichia coli individually expressing twenty-one aminoglycoside resistance enzymes. Plazomicin retained antibacterial activity against 15 of the 17 modifying enzyme-expressing strains tested. Expression of only two of the modifying enzymes, aac(2')-Ia and aph(2″)-IVa, decreased plazomicin potency. On the other hand, expression of 16S rRNA ribosomal methyltransferases results in a complete lack of plazomicin potency. In vitro enzymatic assessment confirmed that AAC(2')-Ia and APH(2")-IVa (aminoglycoside acetyltransferase, AAC; aminoglycoside phosphotransferase, APH) were able to utilize plazomicin as a substrate. AAC(2')-Ia and APH(2")-IVa are limited in their distribution to Providencia stuartii and Enterococci, respectively. These data demonstrate that plazomicin is not modified by a broad spectrum of common aminoglycoside modifying enzymes including those commonly found in Enterobacteriaceae. However, plazomicin is inactive in the presence of 16S rRNA ribosomal methyltransferases, which should be monitored in future surveillance programs.

Cannabidiol (CBD), a Cannabis sativa constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Deutetrabenazine (Austedo, Teva), an approved treatment of chorea in Huntington's disease and tardive dyskinesia in adult patients, is a rationally designed deuterated form of tetrabenazine. Two studies assessed the pharmacokinetics and safety of deutetrabenazine compared with tetrabenazine, and the effects of food on absorption of the deuterated active metabolites, α-dihydrotetrabenazine (α-HTBZ) and β-dihydrotetrabenazine (β-HTBZ). One study was an open-label 2-part study in healthy volunteers; the first part included a crossover single dose of two 15

mg candidate deutetrabenazine formulations in fed and fasted states compared with tetrabenazine 25 mg in the fasted state, and the second part included single and repeated dosing of the commercial formulation of deutetrabenazine (7.5, 15, and 22.5 mg) compared with tetrabenazine 25 mg. The second study was an open-label 5-way crossover study in healthy volunteers (n = 32) to evaluate relative bioavailability of 4 dose levels of the commercial formulation of deutetrabenazine (6, 12, 18, and 24 mg) with a standard meal and 18 mg with a high-fat meal. Both studies confirmed longer half-lives for active metabolites and lower peak-to-trough fluctuations for the sum of the metabolites (total [α+β]-HTBZ) following deutetrabenazine compared with tetrabenazine (3- to 4-fold and 11-fold, respectively) in steady-state conditions. Deutetrabenazine doses estimated to provide total (α+β)-HTBZ exposure comparable to tetrabenazine 25 mg were 11.4-13.2 mg. Food had no effect on exposure to total (α+β)-HTBZ, as measured by AUC. Although the total (α+β)-HTBZ C_{max} of deutetrabenazine was increased by ≈50% in the presence of food, it remained lower than that of tetrabenazine.

Dysregulation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B/mammalian target of rapamycin signaling is common in both indolent and aggressive forms of malignant lymphoma, for which several targeted therapies have been developed. Copanlisib is a highly selective and potent intravenous pan-class I PI3K inhibitor that has demonstrated durable objective responses and a manageable safety profile in heavily pre-treated patients with indolent lymphomas. As a result, copanlisib monotherapy received accelerated approval from the US Food and Drug Administration for the treatment of adults with relapsed follicular lymphoma who have received at least two systemic therapies, and breakthrough designation for patients with pre-treated relapsed or refractory marginal zone lymphoma. Hyperglycemia and hypertension are among the most frequently reported adverse events with copanlisib monotherapy, and are infusion-related, transient, and manageable with standard therapies. Mild diarrhea is also a common adverse event with copanlisib monotherapy; there is no evidence of worsening severity of diarrhea, or serious gastrointestinal toxicities such as colitis or severe liver enzyme elevations, which have been reported with orally administered PI3K inhibitors. The intravenous route of administration and intermittent dosing schedule of copanlisib may support a favorable tolerability profile over continually administered oral alternatives. Ongoing studies of copanlisib in combination with rituximab and standard-of-care chemotherapy in patients with relapsed indolent lymphoma have the potential to support the use of copanlisib in the second-line setting, providing a much-needed additional therapeutic option in this underserved patient population.

Serratia marcescens is an opportunistic pathogen that causes diverse nosocomial infections. *S. marcescens* has developed considerable resistance to different antibiotics and is equipped with an armory of virulence factors. These virulence factors are regulated in *S. marcescens* by an intercellular communication system termed quorum sensing (QS). Targeting bacterial virulence and QS is an interesting approach to mitigating bacterial pathogenesis and overcoming the development of resistance to antimicrobials. In this study, we aimed to evaluate the anti-virulence activities of secnidazole on a clinical isolate of *S. marcescens*. The effects of secnidazole at sub-inhibitory concentrations (sub-MICs) on virulence factors, swarming motility, biofilm formation, proteases, hemolysin activity, and prodigiosin production were evaluated in vitro. Secnidazole's protective activity against *S. marcescens* pathogenesis was assessed in vivo in mice. Furthermore, a molecular docking study was conducted to evaluate the binding ability of secnidazole to the *S. marcescens* SmaR QS receptor. Our findings showed that secnidazole at sub-MICs significantly reduced *S. marcescens* virulence factor production in vitro and diminished its pathogenesis in mice. The *insilico* docking study revealed a great ability of secnidazole to competitively hinder the binding of the autoinducer to the SmaR QS receptor. In conclusion, secnidazole is a promising anti-virulence agent that may be used to control infections caused by *S. marcescens*.

Butylphtalide increases the vascular endothelial growth factor (VEGF) and decreases matrix metalloproteinase (MMP)-9 in animal models of stroke and might be of use in the management of stroke. To explore whether butylphthalide combined with conventional treatment can change

the levels of MMP-9 and VEGF and the National Institutes of Health Stroke Scale (NIHSS) scores of patients with stroke. This was a prospective cohort study involving inpatients admitted to the Jiangxi Provincial People's Hospital (January-June 2019) due to acute cerebral infarction. The patients received conventional treatments with or without butylphthalide. The changes in the NIHSS scores were compared between groups. Plasma MMP-9 and VEGF were measured by enzyme-linked immunosorbent assay. A total of 24 patients were included in the conventional treatment group and 46 in the butylphthalide group. The butylphthalide group showed lower MMP-9 (130 ± 59 vs. 188 ± 65, $p = 0.001$) and higher VEGF (441 ± 121 vs. 378 ± 70, $p = 0.034$) levels on day 6 compared with the conventional treatment group. The changes in MMP-9 and VEGF were significant, starting on day 3 in the butylphthalide group but on day 6 in the conventional treatment group. There were no differences between the two groups in the NIHSS scores at admission and at discharge ($p > 0.05$). The overall response rate was higher in the butylphthalide group compared with the conventional treatment group (63.0 vs. 37.5%, $p = 0.042$).Butylphthalide combined with conventional treatment can decrease MMP-9 levels and increase VEGF levels. The patients showed the reduced NIHSS scores, possibly suggesting some improvement in prognosis after stroke. Still, the conclusions need to be confirmed in a larger sample and in different etiological subtypes of stroke.

In humans, approximately 60 mg of ascorbic acid (AA) breaks down in the body each day and has to be replaced by a dietary intake of 70 mg in women and 90 mg in men to maintain optimal health and AA homeostasis. The breakdown of AA is non-enzymatic and results in oxalate formation. The exact amount of oxalate formed has been difficult to ascertain primarily due to the limited availability of healthy human tissue for such research and the difficulty in measuring AA and its breakdown products. The breakdown of 60 mg of AA to oxalate could potentially result in the formation of up to 30 mg oxalate per day. This exceeds our estimates of the endogenous production of 10-25 mg oxalate per day, indicating that degradative pathways that do not form oxalate exist. In this review, we examine what is known about the pathways of AA metabolism and how oxalate forms. We further identify how gaps in our knowledge may be filled to more precisely determine the contribution of AA breakdown to oxalate production in humans. The use of stable isotopes of AA to directly assess the conversion of vitamin to oxalate should help fill this void.

Acalabrutinib has demonstrated significant efficacy and safety in relapsed chronic lymphocytic leukemia (CLL). Efficacy and safety of acalabrutinib monotherapy were evaluated in a treatment-naive CLL cohort of a single-arm phase 1/2 trial (ACE-CL-001). Adults were eligible for enrollment if chemotherapy was declined or deemed inappropriate due to comorbidities (N = 99). Patients had a median age of 64 years and 47% had Rai stage III/IV disease. Acalabrutinib was administered orally 200 mg once daily, or 100 mg twice daily until progression or intolerance. A total of 99 patients were treated; 57 (62%) had unmutated immunoglobulin heavy-chain variable gene, and 12 (18%) had TP53 aberrations. After median follow-up of 53 months, 85 patients remain on treatment; 14 discontinued treatment, mostly because of adverse events (AEs) (n = 6) or disease progression (n = 3). Overall response rate was 97% (90% partial response; 7% complete response), with similar outcomes among all prognostic subgroups. Because of improved trough BTK occupancy with twice-daily dosing, all patients were transitioned to 100 mg twice daily. Median duration of response (DOR) was not reached; 48-month DOR rate was 97% (95% confidence interval, 90-99). Serious AEs were reported in 38 patients (38%). AEs required discontinuation in 6 patients (6%) because of second primary cancers (n = 4) and infection (n = 2). Grade ≥3 events of special interest included infection (15%), hypertension (11%), bleeding events (3%), and atrial fibrillation (2%). Durable efficacy and long-term safety of acalabrutinib in this trial support its use in clinical management of symptomatic, untreated patients with CLL.

Reduction of intraocular pressure is the only proven method to treat glaucoma. Initial treatment of glaucoma commonly involves using anti-glaucoma medications either as monotherapy or combination therapy. Studies on aqueous humour dynamics have contributed to our

understanding of aqueous outflow mechanisms that have led to the discovery of new drugs. Three new drugs (latanoprostene bunod 0.24%, netarsudil 0.02%, and fixed combination netarsudil 0.02% -latanoprost 0.005%) have been introduced recently in the market with novel mechanisms of action. Latanoprostene bunod 0.024% is a nitric oxide-donating prostaglandin F2α analogue which increases the aqueous outflow both by uveoscleral and trabecular pathways. Netarsudil 0.02% is a potent Rho kinase/norepinephrine transporter inhibitor acting by increasing the trabecular outflow, decreasing the aqueous production, and possibly decreasing the episcleral venous pressure. This review highlights the role of these drugs in the management of glaucoma, with an overview of the major clinical trials on their efficacy, safety, and tolerability.

Data on the efficacy, dosing and safety of letermovir for the compassionate therapeutic use of CMV infections are limited.Clinical and virological efficacy of letermovir was assessed in a retrospective single-centre study of patients who received letermovir for the compassionate therapeutic use of CMV infections. Letermovir initiation yielded prompt treatment response in 7 out of 9 patients (77.7%).Letermovir may be an effective and well tolerated option in the compassionate treatment of CMV infections, although recurrence of CMV and emergence of resistance may be issues.

Monoclonal antibodies (mAbs) are novel, effective therapeutics for the treatment of inadequately controlled severe asthma. Knowledge of the anaphylaxis risks related to different mAbs is essential for their appropriate and safe administration. This study aimed to evaluate the associations between different mAbs and anaphylactic reactions by applying statistical approaches to pharmacovigilance data.This was a retrospective study using data from the US Food and Drug Administration Adverse Event Reporting System database from January 2004 to September 2020. A total of 2006 reports of anaphylaxis related to benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab were obtained through data mining. The clinical characteristics of the cases were analyzed, and the risk signals of anaphylactic reactions and corresponding outcomes were investigated in the five mAbs.

8-chloro-11-{1-[(5-methyl-pyridin-3-yl)meth-yl]piperidin-4-yl-idene}-6,11-di-hydro-5H-benzo[5,6]cyclo-hepta-[1,2-b]pyridine), C26H26ClN3, the dihedral angle between the mean planes of the chloro-phenyl and cyclo-hepta-[1,2-b]pyridinyl rings fused to the cyclo-heptane ring is 56.6 (1)°. The mean planes of the cyclo-hepta-[1,2-b]pyridinyl and 5-methyl-pyridin-3-yl rings are twisted by 64.9 (4)°. The central piperizene group is in a slightly distorted chair configuration. A weak intra-molecular C-H⋯N inter-action is observed between the cyclo-hepta-[1,2-b]pyridinyl and piperidin-4-yl-idene moieties.

To explore the antibacterial spectrum of ozenoxacin and compare its *in vitro* activity with that of other antibacterial agents.In 2010, 10,054 isolates were collected from 128 centers worldwide. Minimum inhibitory concentrations against Gram-positive and Gram-negative isolates were determined for 23 and 13 antibacterial agents, respectively.Ozenoxacin exhibited high *in vitro* activity against susceptible, and methicillin- or levofloxacin-resistant, Gram-positive bacteria. Ozenoxacin was one or two dilutions less active against Enterobacteriaceae isolates, except for *Escherichia coli*, than other quinolones. Ozenoxacin is a potent antimicrobial agent mainly against susceptible and resistant strains of Gram-positive isolates (staphylococci and streptococci), and shows activity against some Gram-negative isolates.

Acyclovir, valacyclovir, and famciclovir are used for the treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. Helicase-primase inhibitors (HPIs) inhibit replication fork progression that separates double DNA strands into two single strands during DNA synthesis. The HPIs amenamevir and pritelivir have novel mechanisms of anti-herpetic action, and their once-daily administration has clinical efficacy for genital herpes. Among HPIs, amenamevir has anti-VZV activity. The concentrations of HSV-1 and VZV required for the 50% plaque reduction of amenamevir were 0.036 and 0.047 μM, respectively. We characterized the

features of amenamevir regarding its mechanism, resistance, and synergism with acyclovir. Its antiviral activity was not influenced by the viral replication cycle, in contrast to acyclovir. A clinical trial of amenamevir for herpes zoster demonstrated its non-inferiority to valacyclovir. To date, amenamevir has been successfully used in over 1,240,000 patients with herpes zoster in Japan. Post-marketing surveillance of amenamevir in Japan reported side effects with significant potential risk identified by the Japanese Risk Management Plan, including thrombocytopenia, gingival bleeding, and palpitations, although none of these were serious. The clinical efficacy and safety profiles of amenamevir were established in patients with herpes zoster. Therefore, amenamevir as an HPI opens a new era of anti-herpes therapy.

Reduction of intraocular pressure is the only proven method to treat glaucoma. Initial treatment of glaucoma commonly involves using anti-glaucoma medications either as monotherapy or combination therapy. Studies on aqueous humour dynamics have contributed to our understanding of aqueous outflow mechanisms that have led to the discovery of new drugs. Three new drugs (latanoprostene bunod 0.24%, netarsudil 0.02%, and fixed combination netarsudil 0.02% -latanoprost 0.005%) have been introduced recently in the market with novel mechanisms of action. Latanoprostene bunod 0.024% is a nitric oxide-donating prostaglandin F2α analogue which increases the aqueous outflow both by uveoscleral and trabecular pathways. Netarsudil 0.02% is a potent Rho kinase/norepinephrine transporter inhibitor acting by increasing the trabecular outflow, decreasing the aqueous production, and possibly decreasing the episcleral venous pressure. This review highlights the role of these drugs in the management of glaucoma, with an overview of the major clinical trials on their efficacy, safety, and tolerability.

Targeted therapies have been a mainstay of the renal cell carcinoma (RCC) treatment paradigm for the better part of two decades. Multikinase inhibitors of the vascular endothelial growth factor receptor tyrosine kinases (VEGF-TKIs) comprise nearly all targeted therapies in RCC, having been prospectively tested through large, multi-institutional phase III trials. Tivozanib is a VEGF-TKI with high selectivity for VEGF receptors 1-3. Tivozanib has been under investigation for nearly 15 years, with a robust portfolio of preclinical and clinical data. This review seeks to characterize tivozanib within the context of RCC by highlighting preclinical and early clinical trials alongside the phase III trials in RCC, TIVO-1, and TIVO-3. We also aim to explore further trials of tivozanib, whether in combination with other agents and/or in differing disease settings, while providing insight into the utility of tivozanib as a clinical tool for the management of RCC.

The anti-leukemia agent forodesine causes cytotoxic overload of intracellular deoxyguanosine triphosphate (dGTP) but is efficacious only in a subset of patients. We report that SAMHD1, a phosphohydrolase degrading deoxyribonucleoside triphosphate (dNTP), protects cells against the effects of dNTP imbalances. SAMHD1-deficient cells induce intrinsic apoptosis upon provision of deoxyribonucleosides, particularly deoxyguanosine (dG). Moreover, dG and forodesine act synergistically to kill cells lacking SAMHD1. Using mass cytometry, we find that these compounds kill SAMHD1-deficient malignant cells in patients with chronic lymphocytic leukemia (CLL). Normal cells and CLL cells from patients without SAMHD1 mutation are unaffected. We therefore propose to use forodesine as a precision medicine for leukemia, stratifying patients by SAMHD1 genotype or expression.

Regorafenib is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of refractory metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GIST) previously treated with imatinib and sunitinib, and unresectable hepatocellular carcinoma (HCC) following progression on sorafenib. Regorafenib was initially approved for mCRC based on improved overall survival (OS) in the randomized, placebo-controlled, phase 3 CORRECT trial, which was confirmed in an expanded population of Asian patients in the randomized, placebo-controlled phase 3 CONCUR trial. Approvals in GIST, and more recently in HCC, were based on the results from the randomized, placebo-controlled, phase 3 GRID and RESORCE trials,

respectively. In this review, we provide a comprehensive summary of the clinical evidence for approval of regorafenib in mCRC, GIST, and HCC, present emerging evidence of regorafenib activity in other tumor types (namely, gastroesophageal cancer, sarcomas, biliary tract cancer, and glioblastoma), and discuss trials in progress within the context of regorafenib's mechanism of action. We describe recent advances and key lessons learned with regorafenib, including the importance of managing common drug-related toxicities using dose-optimization strategies, the search for biomarkers to predict response to treatment, and highlight some of the unaddressed questions and future directions for regorafenib across tumors.

With the advent of new targeted drugs in hematology and oncology patient prognosis is improved. Combination with antifungal prophylaxis challenges clinicians due to pharmacological profiles prone to drug-drug interactions (DDI). Midostaurin is a novel agent for FLT3-TKD/-ITD^{mut}-acute myeloid leukemia (AML) and metabolized via cytochrome P450 3A4 (CYP3A4). Posaconazole is a standard of care antifungal agent used for prophylaxis during induction treatment of AML and a strong CYP3A4 inhibitor. Concomitant administration of both drugs leads to elevated midostaurin exposure. Both drugs improve overall survival at low numbers needed to treat. The impact of CYP3A4-related DDI remains to be determined. Severe adverse events have been observed; however, it remains unclear if they can be directly linked to DDI. The lack of prospective clinical studies assessing incidence of invasive fungal infections and clinical impact of DDI contributes to neglecting live-saving antifungal prophylaxis.
Management strategies to combine both drugs have been proposed, but evidence on which approach to use is scarce. In this review, we discuss several approaches in the specific clinical setting of concomitant administration of midostaurin and posaconazole and give examples from everyday clinical practice. Therapeutic drug monitoring will become increasingly important to individualize and personalize antineoplastic concomitant and antifungal treatment in the context of DDI. Pharmaceutical companies addressing the issue in clinical trials may take a pioneer role in this field. Other recently developed and approved drugs for the treatment of AML likely inhere potential of DDI marking a foreseeable issue in future treatment of this life-threatening disease.

Brigatinib, a next-generation anaplastic lymphoma kinase (ALK) inhibitor, demonstrated superior progression-free survival (PFS) and improved health-related quality of life (QoL) versus crizotinib in advanced ALK inhibitor-naive ALK-positive non-small cell lung cancer (NSCLC) at first interim analysis (99 events; median brigatinib follow-up, 11.0 months) in the open-label, phase III ALTA-1L trial .We report results of the second prespecified interim analysis (150 events).Patients with ALK inhibitor-naive advanced ALK-positive NSCLC were randomly assigned 1:1 to brigatinib 180 mg once daily (7-day lead-in at 90 mg once daily) or crizotinib 250 mg twice daily. The primary end point was PFS as assessed by blinded independent review committee (BIRC). Investigator-assessed efficacy, blood samples for pharmacokinetic assessments, and patient-reported outcomes were also collected.

In the phase 3 PACIFIC study of patients with unresectable stage III NSCLC without progression after chemoradiotherapy, durvalumab demonstrated significant improvements versus placebo in the primary end points of progression-free survival (hazard ratio [HR] = 0.52, 95% confidence interval [CI]: 0.42-65, $p < 0.0001$) and overall survival (OS) (HR = 0.68, 95% CI: 0.53-0.87, $p = 0.00251$), with manageable safety and no detrimental effect on patient-reported outcomes. Here, we report 3-year OS rates for all patients randomized in the PACIFIC study.Patients, stratified by age, sex, and smoking history, were randomized (2:1) to receive durvalumab, 10 mg/kg intravenously every 2 weeks, or placebo for up to 12 months. OS was analyzed by using a stratified log-rank test in the intention-to-treat population. Medians and rates at 12, 24, and 36 months were estimated by the Kaplan-Meier method.As of January 31, 2019, 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively). The median duration of follow-up was 33.3 months. The updated OS remained consistent with that previously reported (stratified HR = 0.69 [95% CI: 0.55-0.86]); the median OS was not reached with durvalumab but was 29.1 months with placebo. The 12-, 24- and 36-

month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively. All secondary outcomes examined showed improvements consistent with previous analyses.Updated OS data from PACIFIC, including 3-year survival rates, demonstrate the long-term clinical benefit with durvalumab after chemoradiotherapy and further establish the PACIFIC regimen as the standard of care in this population.

Intravenous (IV) and subcutaneous (SC) tocilizumab (RoActemra®), an IL-6 receptor antagonist, are approved (± methotrexate) in numerous countries throughout the world, for the treatment of adults with moderate to severe active rheumatoid arthritis (RA). Extensive clinical experience has firmly established the short- and long-term efficacy and safety of tocilizumab [monotherapy or in combination with conventional synthetic DMARDs (csDMARDs)] in adults with early-stage and longer-duration established RA. In the clinical trial and real-world settings, tocilizumab monotherapy or combination therapy provided rapid and sustained improvements in clinical and radiographic outcomes and health-related quality of life. The safety profile of tocilizumab is consistent over time and, in general, is consistent with that of other immunomodulatory agents. This narrative review, written from an EU perspective, summarizes the clinical use of IV and SC tocilizumab in RA. Given its low risk of immunogenicity, the flexibility of IV and SC administration and the convenience of the once-weekly, self-administered, SC regimen, tocilizumab provides an effective treatment for severe, active and progressive RA in adults not previously treated with methotrexate and an effective biologic first- or subsequent-line treatment for moderate to severe active RA in adults who have either responded inadequately to or were intolerant of previous therapy with ≥ 1 csDMARD or TNF inhibitor.

Safety and efficacy of mAbs blocking the IL-6 receptor have been established in RA. This is the first analysis examining safety and tolerability of sarilumab and tocilizumab administered as single or multiple doses in patients with RA within the same study.In ASCERTAIN, patients were randomized 1: 1: 2 to 24 weeks' double-blind sarilumab 150 or 200 mg every 2 weeks s.c. or tocilizumab 4 mg/kg every 4 weeks i.v., increased to 8 mg/kg if clinically indicated. In Study 1309, patients were randomized 1: 1: 1: 1 to single-dose open-label sarilumab 150 or 200 mg s.c. or tocilizumab 4 or 8 mg/kg i.v.In ASCERTAIN, incidence of treatment-emergent adverse events was similar between sarilumab and tocilizumab. The most common treatment-emergent adverse events were the following: sarilumab: neutropenia [6 patients (12.2%) in the 150 mg group and 8 (15.7%) in the 200 mg group], nasopharyngitis [6 (12.2%) and 3 (5.9%)], and injection-site erythema [4 (8.2%) and 4 (7.8%)]; tocilizumab: accidental overdose [9 (8.8%)], upper respiratory tract infection [7 (6.9%)] and nausea [7 (6.9%)]. Laboratory changes in both studies included decreased neutrophils and platelets and increased transaminases and lipids. In Study 1309, incidence of absolute neutrophil count <1.0 giga/l was similar between sarilumab and tocilizumab, and occurred more frequently in the higher dose groups. No association between decrease in absolute neutrophil count and increased incidence of infection was observed in either study.No clinically meaningful differences in treatment-emergent adverse events were observed between sarilumab and tocilizumab. Laboratory changes with sarilumab were within the same range as those with tocilizumab.

Therapeutic options for treating *Mycobacterium abscessus* infections are extremely limited; quinolones are important. The *in vitro* anti-*M. abscessus* activities of nine quinolones, emphasizing sitafloxacin, were investigated. Antimicrobial susceptibility testing was performed on 10 non-tuberculous mycobacterium reference strains and 194 clinical, *M. abscessus* isolates. The activity of sitafloxacin against intracellular *M. abscessus* residing within macrophages was also evaluated. A checkerboard assay was conducted to determine synergy between sitafloxacin and 10 clinically important antibiotics. Among the nine quinolones tested, sitafloxacin exhibited the greatest anti-*M. abscessus* activity with MIC_{50} and MIC_{90} of 1 and 2 mg/L, respectively. Sitafloxacin exerted a bacteriostatic effect on *M. abscessus* and inhibited the intracellular growth of *M. abscessus* at concentrations equivalent to clarithromycin. No antagonism between sitafloxacin and 10 clinically important anti-*M. abscessus* antibiotics was evident. In summary,

sitafloxacin exhibited a significant advantage relative to other quinolones in inhibiting the growth of *M. abscessus in vitro*, suggesting the potential inclusion of sitafloxacin in new strategies to treat *M. abscessus* infections.

Depression is the most common psychiatric condition encountered in elderly people. The present paper intended to first review past epidemiological studies on depression in late life and secondly to investigate the symptomatological characteristics of depression in the elderly. The author also report significant results of a therapeutic approach to late-life depression, including antidepressant drug treatment and non-convulsive electric shock therapy. Previous epidemiological studies on prevalence rate of late life depression can be divided into two distinct groups according to their different methodologies including subjective and objective evaluations. Approximately 30% subjectively evaluated and 3% objectively evaluated in elderly people older than 65 years of age were depressed with depressed women outnumbering men approximately 2 to 1. Comparisons of the symptomatological characteristics were made in an extremely wide series of 104 depressed in-patients. Depressed patients with hypochodriacal complaints, pseudo-dementia, delusion and suicidal urges increased with aging. Depressed patients with a genetic factor decreased with aging, suggesting that the depressed patients in late life seems to have multiple etiological factors. We intended to correlate the plasma levels of various antidepressant drugs to the age of the depressed patients. There were significant positive correlations between the plasma levels and the age in patients with tricyclic antidepressant (amoxapine, dothiepin) treatment while on the other hand, no significant correlation was found between the two values in the patients with non-tricyclic antidepressant (setiptiline) treatment. These results suggest that non-tricyclic antidepressant drug should be selected for the treatment of depression in the elderly

The global spread of antibacterial-resistant strains, especially methicillin-resistant Staphylococcus aureus (MRSA) for acute bacterial skin and skin structure infections (ABSSSIs), has driven the need for novel antibacterials. Delafloxacin [Quofenix™ (EU); Baxdela® (USA)], a new fluoroquinolone (FQ), has a unique chemical structure that enhances its antibacterial activity in acidic environments such as occurs in ABSSSIs (including S. aureus infections).
Delafloxacin (intravenous and oral formulations) is approved in several countries for the treatment of adults with ABSSSIs (featured indication). In intent-to-treat analyses in pivotal phase 3 trials in adults with ABSSSIs, including those with comorbid disease, intravenous delafloxacin monotherapy (± oral switch after six doses) twice daily was noninferior to intravenous vancomycin + aztreonam for primary endpoints, as specified by the FDA (objective response rate at 48-78 h after initiation of therapy) and the EMA [investigator-assessed clinical cure rate at the follow-up visit at day 14 (± 1 day)]. Delafloxacin was generally well tolerated, with most treatment-related adverse events mild to moderate in severity and few patients discontinuing treatment because of these events. Relative to vancomycin + aztreonam (a non-FQ regimen), delafloxacin treatment was not associated with an increased risk of FQ-associated AEs of special interest. Given its unique chemical structure that confers novel properties relative to other FQ and its broad spectrum of activity against common clinically relevant Gram-positive pathogens, including against MRSA strains (± FQ-resistance mutations), and Gram-negative pathogens, intravenous delafloxacin (± oral switch) provides a novel emerging option for the treatment of adult patients with ABSSSIs.

Everolimus (Afinitor) is an inhibitor of mammalian target of rapamycin. Polmacoxib (Acelex) is a nonsteroidal anti-inflammatory drug that belongs to the cyclooxygenase-2 (COX-2) inhibitor family and is mainly used for treatment of arthritis. Intestinal perforation has not been reported previously as a complication of everolimus, and perforation of the lower intestinal tract caused by a selective COX-2 inhibitor is extremely rare. We present here a case of colon perforation that occurred after use of polmacoxib in a metastatic breast cancer patient who had been treated with everolimus for the preceding six months.

Calcific aortic valve disease (CAVD) accompanies inflammatory cell infiltration, fibrosis, and ultimately calcification of the valve leaflets. We previously demonstrated that dipeptidyl

peptidase-4 (DPP-4) is responsible for the progression of aortic valvular calcification in CAVD animal models. As evogliptin, one of the DPP-4 inhibitors displays high specific accumulation in cardiac tissue, we here evaluated its therapeutic potency for attenuating valvular calcification in CAVD animal models. Evogliptin administration markedly reduced calcific deposition accompanied by a reduction in proinflammatory cytokine expression in endothelial nitric oxide synthase-deficient mice in vivo, and significantly ameliorated the mineralization of the primary human valvular interstitial cells (VICs), with a reduction in the mRNA expression of bone-associated and fibrosis-related genes in vitro. In addition, evogliptin ameliorated the rate of change in the transaortic peak velocity and mean pressure gradients in our rabbit model as assessed by echocardiography. Importantly, evogliptin administration in a rabbit model was found to suppress the effects of a high-cholesterol diet and of vitamin D2-driven fibrosis in association with a reduction in macrophage infiltration and calcific deposition in aortic valves. These results have indicated that evogliptin prohibits inflammatory cytokine expression, fibrosis, and calcification in a CAVD animal model, suggesting its potential as a selective therapeutic agent for the inhibition of valvular calcification during CAVD progression.

Pancreatic cancer (PC) is one of the most common human malignancies worldwide and remains a major clinical challenge. Here, we found that benproperine phosphate (BPP), a cough suppressant, showed a significant anticancer effect on PC both in vitro and in vivo via the induction of autophagy-mediated cell death. Mechanistic studies revealed that BPP triggered AMPK/mTOR-mediated autophagy initiation and disturbed Ras-related protein Rab-11A (RAB11A)-mediated autophagosome-lysosome fusion, resulting in excessive accumulation of autophagosomes. Inhibition of autophagy or overexpression of RAB11A partially reversed BPP-induced growth inhibition in PC cells, suggesting that BPP might induce lethal autophagy arrest in PC cells. In conclusion, our results identify BPP as a potent antitumor agent for PC via the induction of autophagy arrest, therefore providing a new potential therapeutic strategy for the treatment of PC.

Patients who are chronically infected with hepatitis C virus (HCV) and who do not have a sustained virologic response after treatment with regimens containing direct-acting antiviral agents (DAAs) have limited retreatment options.

We conducted two phase 3 trials involving patients who had been previously treated with a DAA-containing regimen. In POLARIS-1, patients with HCV genotype 1 infection who had previously received a regimen containing an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive either the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the protease inhibitor voxilaprevir (150 patients) or matching placebo (150 patients) once daily for 12 weeks. Patients who were infected with HCV of other genotypes (114 patients) were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group. In POLARIS-4, patients with HCV genotype 1, 2, or 3 infection who had previously received a DAA regimen but not an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive sofosbuvir-velpatasvir-voxilaprevir (163 patients) or sofosbuvir-velpatasvir (151 patients) for 12 weeks. An additional 19 patients with HCV genotype 4 infection were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group. In the three active-treatment groups, 46% of the patients had compensated cirrhosis. In POLARIS-1, the rate of sustained virologic response was 96% with sofosbuvir-velpatasvir-voxilaprevir, as compared with 0% with placebo. In POLARIS-4, the rate of response was 98% with sofosbuvir-velpatasvir-voxilaprevir and 90% with sofosbuvir-velpatasvir. The most common adverse events were headache, fatigue, diarrhea, and nausea. In the active-treatment groups in both trials, the percentage of patients who discontinued treatment owing to adverse events was 1% or lower.

Hepatitis C virus (HCV) infection is a major cause of end-stage liver disease, including decompensated cirrhosis and hepatocellular carcinoma. Over 95% of patients with HCV

infection have achieved sustained virologic response at 12 weeks under the treatment of several pan-genotypic regimens approved for patients with HCV infection. The glecaprevir/pibrentasvir (G/P) regimen has some features that distinguish it from others and is the only 8-week regimen approved for treatment-naive patients and patients experienced in regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, without an HCV NS3/4A protease inhibitor or NS5A inhibitor (except those with genotype 3). This review aims to summarize the efficacy and safety of G/P in HCV-infected patients from clinical trials and real-world studies, including those who have historically been considered difficult to cure.

The World Health Organization estimates that 71 million people worldwide have chronic hepatitis C viral infection. A major challenge is the overall lack of public awareness of hepatitis C, particularly among infected people of their infection status. Chronic hepatitis C infection is associated with advanced liver disease, is the main cause of hepatocellular carcinoma and causes many extra-hepatic manifestations. The existence of seven viral genotypes complicates targeting of treatment. Recent years have seen the approval of many direct acting antivirals targeted at hepatitis C virus non-structural proteins. These have revolutionized therapy as they allow achievement of extremely high sustained virologic responses. Of great significance is the development of pan-genotypic drug combinations, including the NS3/4A-NS5A inhibitor combinations sofosbuvir-velpatasvir and glecaprevir-pibrentasvir. However, resistance-associated mutations can result in failure of these treatments in a small number of patients. This, combined with the high costs of treatment, highlights the importance of continued research into effective anti-hepatitis C therapies, for example aimed at viral entry. Recent developments include identification of the potential of low-cost anti-histamines for repurposing as inhibitors of hepatitis C viral entry. In this review we focus on molecular biology of hepatitis C virus, and the new developments in hepatitis C treatment.

Treatment of latent tuberculosis (TB) infection is an important component of TB control programs in both high- and low-prevalence countries. Clinical trials of treatment of latent TB conducted over several decades have demonstrated that preventive treatment can reduce the risk of developing active TB up to 90%. Although 9 months of daily, self-administered isoniazid has been the most widely used and recommended regimen for the treatment of latent infection, other regimens such as 3 months of daily isoniazid and rifampin, or 4 months of daily rifampin alone have also been recommended and used. Most recently, a 12-dose regimen of once-weekly isoniazid and rifapentine has been shown to be noninferior to 9 months of daily isoniazid in a large and well conducted clinical trial. Adoption of such a regimen on a large scale could have significant implications for TB elimination efforts.

single-arm, open-label phase 2 study of the PARP inhibitor (PARPi) rucaparib in relapsed high-grade ovarian carcinoma. In this post hoc exploratory biomarker analysis of pre- and post-platinum ARIEL2 samples, RAD51C and RAD51D mutations and high-level BRCA1 promoter methylation predict response to rucaparib, similar to BRCA1/BRCA2 mutations. BRCA1 methylation loss may be a major cross-resistance mechanism to platinum and PARPi. Genomic scars associated with homologous recombination deficiency are irreversible, persisting even as platinum resistance develops, and therefore are predictive of rucaparib response only in platinum-sensitive disease. The RAS, AKT, and cell cycle pathways may be additional modulators of PARPi sensitivity.

Secondary metabolites are well known for their ability to impede other microorganisms. Reanalysis of a screen of natural products using the Caenorhabditis elegans-Candida albicans infection model identified twelve microbial secondary metabolites capable of conferring an increase in survival to infected nematodes. In this screen, the two compound treatments conferring the highest survival rates were members of the epipolythiodioxopiperazine (ETP) family of fungal secondary metabolites, acetylgliotoxin and a derivative of hyalodendrin. The abundance of fungal secondary metabolites indentified in this screen prompted further studies investigating the interaction between opportunistic pathogenic fungi and Aspergillus fumigatus,

because of the ability of the fungus to produce a plethora of secondary metabolites, including the well studied ETP gliotoxin. We found that cell-free supernatant of A. fumigatus was able to inhibit the growth of Candida albicans through the production of a secreted product.
Comparative studies between a wild-type and an A. fumigatus ΔgliP strain unable to synthesize gliotoxin demonstrate that this secondary metabolite is the major factor responsible for the inhibition. Although toxic to organisms, gliotoxin conferred an increase in survival to C. albicans-infected C. elegans in a dose dependent manner. As A. fumigatus produces gliotoxin in vivo, we propose that in addition to being a virulence factor, gliotoxin may also provide an advantage to A. fumigatus when infecting a host that harbors other opportunistic fungi.

Proton pump inhibitors (PPIs) are used extensively for the treatment of gastric acid-related disorders, often over the long term, which raises the potential for clinically significant drug interactions in patients receiving concomitant medications. These drug-drug interactions have been previously reviewed. However, the current knowledge is likely to have advanced, so a thorough review of the literature published since 2006 was conducted. This identified new studies of drug interactions that are modulated by gastric pH. These studies showed the effect of a PPI-induced increase in intragastric pH on mycophenolate mofetil pharmacokinetics, which were characterised by a decrease in the maximum exposure and availability of mycophenolic acid, at least at early time points. Post-2006 data were also available outlining the altered pharmacokinetics of protease inhibitors with concomitant PPI exposure. New data for the more recently marketed dexlansoprazole suggest it has no impact on the pharmacokinetics of diazepam, phenytoin, theophylline and warfarin. The CYP2C19-mediated interaction that seems to exist between clopidogrel and omeprazole or esomeprazole has been shown to be clinically important in research published since the 2006 review; this effect is not seen as a class effect of PPIs. Finally, data suggest that coadministration of PPIs with methotrexate may affect methotrexate pharmacokinetics, although the mechanism of interaction is not well understood. As was shown in the previous review, individual PPIs differ in their propensities to interact with other drugs and the extent to which their interaction profiles have been defined. The interaction profiles of omeprazole and pantoprazole sodium (pantoprazole-Na) have been studied most extensively. Several studies have shown that omeprazole carries a considerable potential for drug interactions because of its high affinity for CYP2C19 and moderate affinity for CYP3A4. In contrast, pantoprazole-Na appears to have lower potential for interactions with other medications. Lansoprazole and rabeprazole also seem to have a weaker potential for interactions than omeprazole, although their interaction profiles, along with those of esomeprazole and dexlansoprazole, have been less extensively investigated. Only a few drug interactions involving PPIs are of clinical significance. Nonetheless, the potential for drug interactions should be considered when choosing a PPI to manage gastric acid-related disorders. This is particularly relevant for elderly patients taking multiple medications, or for those receiving a concomitant medication with a narrow therapeutic index.

We devised a new separation technique for the protein, "affinophoresis," which is based on its specific affinity and utilizes electrophoresis. This technique requires a carrier macromolecule, "affinophore," which contains both an affinity ligand for a certain protein and many charges, either positive or negative, in order to migrate rapidly in an electric field. When a mixture of proteins is electrophoresed in the presence of the affinophore, the protein having an affinity with the ligand will form a complex with the affinophore. This results in a change in the apparent electrophoretic mobility. If the protein is sufficiently accelerated, we can separate it from other materials. A cationic affinophore for trypsin was prepared. Soluble dextran MW approximately 10,000) was coupled with a DEAE-group and m-aminobenzamidine, a competitive inhibitor of trypsins. Electrophoresis of trypsins from several origins on agarose gel plates in the presence of the affinophore showed that affinophoresis actually occurred. The electrophoretic mobilities of trypsins increased towards the cathode, the same direction as the affinophore movement. The presence of leupeptin and treatment of the trypsins with TLCK suppressed the effect of the affinophore. Streptomyces griseus trypsin, contained in Pronase, was easily separated and detected. This procedure is distinct from affinity chromatography and so-called affinity

electrophoresis in that the support of the affinity ligand moves, and has advantages especially for analytical purposes: for example, the detection of specific molecules regardless of their isoelectric points.

Acipimox, a nicotinic acid derivative in clinical use for the treatment of hyperlipidaemia, incorporates a free carboxylic acid and an N-oxide moiety, functionalities known to interact with the metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1) and inhibit its activity. Herein we report that acipimox acts as a low micromolar CA inhibitor (CAI) against most human (h) isoforms possessing catalytic activity, hCA I - XIV. By using computational techniques (docking and molecular dynamics simulations), we propose that acipimox coordinates through its carboxylate group to the zinc ion from the enzyme active site cavity, whereas the N-oxide group is hydrogen-bonded to the proton shuttle His residue in some isoforms (hCA I) or to active site Thr or Gln residues in other isoforms (hCA II, III, IV, VII, etc). As some CA isoforms are involved in lipogenesis, these data may be useful for the design of more effective CAIs with antiobesity activity.

Few trials have examined rates of hypersensitivity reactions (HSRs) with intravenous iron formulations used to treat iron deficiency anemia (IDA). This randomized, multicenter, double-blind clinical trial compared the safety, and efficacy of ferumoxytol versus ferric carboxymaltose (FCM), focusing on rates of HSRs and hypotension as the primary end point. Patients with IDA of any etiology in whom oral iron was unsatisfactory or intolerable received ferumoxytol (n = 997) or FCM (n = 1000) intravenously over ≥15 minutes on days 1 and 8 or 9 for total respective doses of 1.02 g and 1.50 g. Composite incidences of moderate-to-severe HSRs, including anaphylaxis, or moderate-to-severe hypotension from baseline to week 5 (primary safety end point) were 0.6% and 0.7% in the ferumoxytol and FCM groups, respectively, with ferumoxytol noninferior to FCM. No anaphylaxis was reported in either group. The secondary safety end point of incidences of moderate-to-severe HSRs, including anaphylaxis, serious cardiovascular events, and death from baseline to week 5 were 1.3% and 2.0% in the ferumoxytol and FCM groups, respectively (noninferiority test $P < .0001$). Least-squares mean changes in hemoglobin at week 5 were 1.4 g/dL and 1.6 g/dL in the ferumoxytol and FCM groups, respectively (noninferiority test $P < .0001$). Incidence of hypophosphatemia was 0.4% for ferumoxytol and 38.7% for FCM.

The reduction of survival motor neuron (SMN) protein causes spinal muscular atrophy (SMA), an autosomal recessive neuromuscular disease. Nusinersen is an antisense oligonucleotide, approved by the FDA, which specifically binds to the repressor within SMN2 exon 7 to enhance exon 7 inclusion and augment production of functional SMN protein. Nusinersen is the first new oligonucleotide-based drug targeting the central nervous system for the treatment of SMA. This review of nusinersen will discuss its action mechanism, cellular uptake, trafficking mechanisms, and administration approaches to cross the blood-brain barrier. Furthermore, nusinersen clinical trials will be assessed in terms of pharmacokinetics, tolerability and safety, the clinical outcomes of multiple intrathecal doses, and a discussion on the primary and secondary endpoints.

This Hospital Pharmacy feature is extracted from Off-Label Drug Facts, a publication available from Wolters Kluwer Health. Off-Label Drug Facts is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made.

Imolamine is a coronary vasodilator, which is used in the treatment of angina pectoris and as a local anesthetic. Imolamine has been shown to produce in animals coronary vasodilation, local anaesthesia, analgesia and a papaverine like action in duodenal preparations. Imolamine increased the tone of uterus and ileum and this was accompanied by a reduction in amplitude of

contraction. The response of the stomach tissue to imolamine was similar to that of butalamine and aminophylline, i.e. a relaxant action on smooth muscle. Imolamine has a variable action on tone, producing an increase in ileum and uterus and a decrease in stomach. Imolamine is able to cause severe cytolytic hepatitis.

Drug induced lichen planus like eruption is an uncommon cutaneous adverse effect of several drugs. This appears symmetric eruption of erythematous or violaceous plaques resembling lichen planus on the trunk and extremities. A 50-year-old male presented with scaly, violaceous plaques and dusky brown macules on whole body. For four months, the patient was treated with olmutinib, an oral, third-generation epidermal growth factor receptor-tyrosine kinase inhibitor. In May 2016, olmutinib received its first global approval in South Korea for the treatment of patients with locally advanced or metastatic epidermal growth factor receptor T790M mutation-positive non-small cell lung cancer. The biopsy specimen from the patient showed features of lichen planus. We diagnosed him with olmutinib-induced lichen planus like eruption. He was treated with oral methylprednisolone and topical desoxymethasone 0.25% ointment. At the same time, olmutinib dose was decreased to three-fourths of this patient's starting dose. After that, the cutaneous lesions improved.

Although imatinib has dramatically improved major outcomes in patients with chronic myeloid leukemia (CML), there are newer tyrosine kinase inhibitors (TKIs) approved worldwide for the treatment of resistant cases, and two second-generation TKIs (dasatinib, nilotinib) are approved in some nations for treating patients in the upfront setting. Radotinib (IY5511HCL, *Supect*®) is a novel and selective second-generation BCR-ABL1 TKI, which is currently approved in Korea for the treatment of patients with CML both in the upfront and salvage settings. This review mainly focuses on the clinical potential of radotinib in patients with CML in chronic phase in terms of efficacy and safety.

An increasing number of men are being diagnosed with hypogonadism. While many benefit from testosterone supplementation therapy, others who do not meet the criteria for hormone supplementation have turned to dietary adjuncts as a way or gaining improvements in libido, energy, and physical performance. These oral adjunct medications include controlled substances such as androstenedione, androstenediol as well as other "over-the-counter" options like DHEA (dehydroepiandrosterone) and herbal remedies like Tribulus terrestris This review will focus on the use of these adjunct medications in isolation, or in combination with testosterone supplementation therapy as well as the biochemical nature of the supplements, the results of scientific trials as well as the side effects that limit their use. At the end of this review, physicians will have an improved understanding of the popular testosterone adjuncts being used currently as well as the availability of these substances and how they are used.

Lenvatinib, a multi-target tyrosine kinase inhibitor (TKI), is an emerging first-line therapy for hepatocellular carcinoma (HCC). Its application has changed the status of sorafenib as the only first-line TKI treatment for HCC for more than a decade. Evidence has shown that lenvatinib possesses antitumor proliferation and immunomodulatory activity in preclinical studies. In comparison, lenvatinib was non-inferior to sorafenib in overall survival (OS), and even shows superiority with regard to all the secondary efficacy endpoints. Immune-checkpoint inhibitors(ICIs)are now being incorporated into HCC treatment. Positive outcomes have been achieved in the combination of lenvatinib plus ICIs, bringing broader prospects for HCC. This review presents an overview on the therapeutic mechanisms and clinical efficacy of lenvatinib in HCC, and we discuss the future perspectives of lenvatinib in HCC management with focus on biomarker-guided precision medicine.

Ciprofibrate (CIP) is a highly lipophilic and poorly water-soluble drug, typically used for dyslipidemia treatment. Although it is already commercialized in capsules, no previous studies report its solid-state structure; thus, information about the correlation with its physicochemical properties is lacking. In parallel, recent studies have led to the improvement of drug

administration, including encapsulation in polymeric nanoparticles (NPs). Here, we present CIP's crystal structure determined by PXRD data. We also propose an encapsulation method for CIP in micelles produced from Pluronic P123/F127 and PEO-*b*-PCL, aiming to improve its solubility, hydrophilicity, and delivery. We determined the NPs' physicochemical properties by DLS, SLS, ELS, SAXS and the loaded drug amount by UV-Vis spectroscopy. Micelles showed sizes around 10-20 nm for Pluronic and 35-45 nm for the PEO-*b*-PCL NPs with slightly negative surface charge and successful CIP loading, especially for the latter; a substantial reduction in ζ-potential may be evidenced. For Pluronic nanoparticles, we scanned different conditions for the CIP loading, and its encapsulation efficiency was reduced while the drug content increased in the nanoprecipitation protocol. We also performed in vitro release experiments; results demonstrate that probe release is driven by Fickian diffusion for the Pluronic NPs and a zero-order model for PEO-*b*-PCL NPs.

Taliglucerase alfa is an enzyme replacement therapy (ERT) approved for treatment of adult and paediatric patients with Type 1 Gaucher disease (GD) in several countries and the first plant cell-expressed recombinant therapeutic protein approved by the US Food and Drug Administration for humans. Here, we review the findings across six key taliglucerase alfa clinical studies. A total of 33 treatment-naïve adult patients were randomized to taliglucerase alfa 30 U/kg or 60 U/kg in a 9-month, multicentre, randomized, double-blind, parallel-group, dose-comparison pivotal study, after which eligible patients continued into two consecutive extension studies; 17 treatment-naïve adult patients completed 5 total years of treatment with taliglucerase alfa. In the only ERT study focused on exclusively paediatric patients with GD, 11 treatment-naïve children were randomized to taliglucerase alfa 30 U/kg or 60 U/kg in a 12-month, multicentre, double-blind study; nine completed 3 total years of treatment in a dedicated paediatric extension study. The effect of switching patients from imiglucerase to taliglucerase alfa was also investigated in a separate 9-month study that included 26 adults and five children; 10 adults completed a total of 3 years and two children completed a total of 2.75 years of taliglucerase alfa treatment in the extension studies. All studies evaluated safety and spleen volume, liver volume, platelet count, haemoglobin concentration, and biomarkers as measures of efficacy. Detailed results from baseline through the end of these studies are presented. Taliglucerase alfa was well tolerated, and adverse events were generally mild/moderate in severity and transient. Treatment with taliglucerase alfa resulted in improvements (treatment-naïve patients) or stability (patients switched from imiglucerase) in visceral, haematologic, and biomarker parameters. Together, this comprehensive data set supports the treatment of adult and paediatric patients with GD who are naïve to ERT or who have previously been treated with imiglucerase.

Maximal pupillary miosis was obtained with single topical applications of cholinomimetic drugs in therapeutic concentrations to normal human subjects. When the pupil had recovered from the miosis, there remained a reduced light reflex response of 22.7% at 24 h after aceclidine, 18.0% at 31 h after pilocarpine, 10.3% at 48 h after physostigmine and 4.9% at 7 h after arecoline. This reduced sensitivity to light was accompanied by an overshoot of the resting pupil diameter and, after aceclidine miosis, a reduced response to a second application of miotic. Similar findings were observed in glaucoma patients following withdrawal of chronic pilocarpine therapy.It is suggested that the slowly reversible after-effects of acute and chronic administration of cholinomimetic miotics can be explained by desensitization of iris sphincter cholinoceptors.

We present the case of a 73-year-old man with IgA vasculitis after administration of acenocoumarol, confirmed by anatomopathological study. He had cutaneous, joint and renal involvement. With the reintroduction of the drug, the clinical manifestations worsened. They were completely resolved with its suspension, without additional maintenance treatment.

Acetarsone is a pentavalent arsenical compound with antiprotozoal and antihelmintic properties. It was first discovered in 1921 at Pasteur Institute by Ernest Fourneau, and sold under the brand name Stovarsol (fourneau is the French word for stove). Before stovarsol was used in the treatment of congenital syphilis, it had already been used in other diseases : amoebiasis, acquired

syphilis, yaws, trypanosomiasis and malaria, and a formidable list of toxic manifestations can be compiled from the literature. Bender (I927) recorded six cases of poisoning with malaise, fever, cedema, jaundice, diarrhoea, albuminuria, bronchitis, coryza and skin troubles, such as diffuse erythema, dryness and pruritus. Of 232 cases of amoebiasis treated by Brown (I935) without a death, thirteen (5.6%) had toxic erythemata, some of them so severe as to amount to exfoliative dermatitis. Although its mechanism of action is not fully known, acetarsone may bind to protein-containing sulfhydryl groups located in the parasite, thereby forming lethal As-S bonds. This may prevent their functioning and eventually kill the parasite.

Acetoxolone is a drug used for peptic ulcer and gastroesophageal reflux disease. It is an acetyl derivative of glycyrrhetinic acid.

Olaratumab is a monoclonal antibody that recently received accelerated approval for the treatment of advanced soft-tissue sarcomas in combination with doxorubicin for a histologic subtype in which anthracycline-containing regimens is appropriate and disease is not amenable to curative surgery or radiotherapy. It inhibits platelet-derived growth factor receptor alpha, leading to the inhibition of tumor cell proliferation, angiogenesis, and metastasis. In a phase II clinical trial, olaratumab in combination with doxorubicin met its predefined primary endpoint of improving progression-free survival and secondary endpoint of overall survival compared to doxorubicin monotherapy in patients with advanced soft-tissue sarcoma. Common adverse events associated with the combination of olaratumab and doxorubicin include nausea, mucositis, neutropenia, and infusion-related reactions

Fenofibrate, which is a PPAR-alfpha agonist, increases the level of sulfatide. In this letter we hypothesize on the background of various findings that this is beneficial against COVID-19. Fenofibrate has been used for decades against hypercholesterolemia and has no serious side effects. Therefore, a trial giving fenofibrate to patients with corona virus infection is recommended.

Chloroxylenol (CHL) is an antimicrobial ingredient that is frequently used in antiseptics/disinfectants for skin (e.g. hand soap) and non-living surfaces. CHL is an alternative to triclosan and triclocarban, the use of which has recently been banned in some countries. Accordingly, the more widespread use of CHL may significantly increase its occurrence and level in aquatic environments in the near future, eventually resulting in potential ecological risks. Wastewater treatment plants (WWTPs) may be a point source of CHL in natural environments due to extensive discharge through urban waste stream disposal. While the satisfactory removal of CHL in WWTPs is critical for maintaining healthy aquatic ecosystems, the extent of CHL removal and whether CHL causes system upset/failure in WWTPs currently remain unknown. In the present study, we conducted bioreactor operation and batch experiments to investigate the fate and effects of CHL and elucidate the mechanisms underlying degradation at various levels from environmentally relevant to high levels (0.5-5 mg L^{-1}). Bioreactors partially removed CHL (44-87%) via a largely biological route. Microbial association networks constructed using 16S rRNA gene sequencing data revealed selective enrichment and a correlation between Sphingobium and CHL, implying its involvement in the biological breakdown of CHL through dehalogenation and ring hydroxylation pathways. The present results provide insights into the behavior and effects of CHL in activated sludge communities and important information for the sustainable management of CHL that may be an emerging issue in the urban water cycle.

Sports nutrition supplements have previously been reported to contain undeclared doping substances. The use of such supplements can lead to general health risks and may give rise to unintentional doping violations in elite sports. To assess the prevalence of doping substances in a range of high-risk sports nutrition supplements available from Dutch web shops. A total of 66 sports nutrition supplements - identified as potentially high-risk products claiming to modulate hormone regulation, stimulate muscle mass gain, increase fat loss, and/or boost energy - were selected from 21 different brands and purchased from 17 web shops. All products were analyzed

for doping substances by the UK life sciences testing company LGC, formerly known as the Laboratory of the Government Chemist, using an extended version of their ISO17025 accredited nutritional supplement screen. A total of 25 out of the 66 products (38%) contained undeclared doping substances, which included high levels of the stimulants oxilofrine, β-methylphenethylamine (BMPEA) and N,β-dimethylphenethylamine (NBDMPEA), the stimulant 4-methylhexan-2-amine (methylhexaneamine, 1,3-dimethylamylamine, DMAA), the anabolic steroids boldione (1,4-androstadiene-3,17-dione) and 5-androstene-3β,17α-diol (17α-AED), the beta-2 agonist higenamine and the beta-blocker bisoprolol. Based upon the recommended dose and the potential variability of analyte concentration, the ingestion of some products identified within this study could pose a significant risk of unintentional doping violations. In addition to inadvertent doping risks, the prescribed use of 3 products (4.5%) could likely impose general health risks.

A method was developed to quantify the "antikeratinizing" effects of various retinoids (all-trans-retinoic acid, 13-cis-retinoic acid, motretinide, etretinate) in rhino mouse skin, which contains many keratinized pilosebaceous structures or horn-filled utriculi. Mean utriculus diameters in whole mount epidermis were determined and dose-response relationships were constructed after topical or oral administration of test retinoids. All-trans-retinoic acid was 3.7x, 12.5x, and 50x more potent than 13-cis-retinoic acid, etretinate, and motretinide, respectively, after topical administration. Administered orally, all-trans-retinoic acid was 2.3x more potent than 13-cis-retinoic acid. At 5 mg/kg, each retinoid produced a significant reduction in utriculus size. The rhino mouse model represents a novel and useful assay to quantify antikeratinizing activity and potency differences of biologically active retinoids.

This study sought to examine whether the administration of quinfamide at 3- or 6-month intervals diminished the frequency of Entamoeba histolytica cysts in stool samples compared to controls. The prospective, longitudinal, randomized, single-blind study examined children from six primary schools in Celaya and Neutla, Guanajuato. Of the 1,524 students in these schools, we selected participants for the study as follows: Children were included in the study if their parents agreed in writing to the study and if the children demonstrated evidence of E. histolytica cysts after a parasitoscopic analysis by concentration (PSC) in three samples over consecutive days using Faust"s method. Those included in the study received a single 4.3-g/kg dose of quinfamide, and we performed PSC on days 5, 6, and 7 following dose administration to examine whether quinfamide had affected the presence of the cysts. The study participants who tested negative for cysts were divided into three groups: Group 1 had 102 patients who underwent quinfamide treatment and three CPS analyses after the 12 months of the study; Group 2 had 98 subjects who underwent the quinfamide treatment and three CPS analyses at months 3, 6, 9, and 12 after their entrance into the study; and Group 3 had 102 patients, who underwent the quinfamide treatment and series of three CPS analyses at months 6 and 12 of the study. All participants received the dose of quinfamide after providing stool samples and after a clinical gastrointestinal history was obtained. Further clinical gastrointestinal data were collected 5 days after the quintamide dose was administered. We used EpiInfo 6.0 for statistical analysis, calculating c2 and p values for the clinical data and the CPS data after the 12 months concluded. Of the initial samples of 1,524 subjects, 308 (20.2%) had Entamoebic cysts. Of these, six were further eliminated because they did not meet the inclusion requirements. At the conclusion of the study, Group 1 presented with 37.6% of subjects still testing positive for cysts; of Group 2, 12.5% tested positive; and in Group 3, 23.5% of participants tested positive for cysts (chi2 = 16.8; df = 2; $p = 0.0002$). For comparisons of groups 1 and 2 and 1 and 3, $p < 0.05$; for the comparison of groups 2 and 3, $p > 0.05$. We conclude that antiamoebic chemoprophylaxis can be a choice for control of amoebic infection where personal hygiene and food consumption habits are not improving.

A new spectrofluorometric method is described for the determination of metacycline (MC), based on modified enzyme-amplified lanthanide luminescence. Under the optimum conditions, Eu3+-MC forms a ternary complex with lysozyme in close proximity. Then lysozyme can

remarkably enhance the characteristic fluorescence intensity of Eu3+ at 612 nm in metacycline-Eu3+ binary complex. The enhanced fluorescence intensity is in proportion to the concentration of MC. The limit of detection is 1.6 x 10(-8) mol L(-1), with a linear range from 6.2 x 10(-6) to 1.7 x 10(-5) mol L(-1). Interferences of other coexisting substances were studied. The developed method was successfully applied to the determination of MC in serum and urine samples. The mechanism of fluorescence enhancement was also studied.

Tibezonium iodide (or **tibenzonium iodide**) is an antiseptic for use in the mouth. It is a salt consisting of a lipophilic quaternary ammonium cation and iodide as the counterion.

Age-related cardiovascular disease is the leading cause of death in elderly populations. Coxibs, including celecoxib, valdecoxib, etoricoxib, parecoxib, lumiracoxib, and rofecoxib, are selective cyclooxygenase-2 (COX-2) inhibitors used to treat osteoarthritis and rheumatoid arthritis. However, many coxibs have been discontinued due to adverse cardiovascular events. COX-2 contains cyclooxygenase (COX) and peroxidase (POX) sites. COX-2 inhibitors block COX activity without affecting POX activity. Recently, quercetin-like flavonoid compounds with OH groups in their B-rings have been found to serve as activators of COX-2 by binding the POX site. Galangin-like flavonol compounds serve as inhibitors of COX-2. Interestingly, nabumetone, flurbiprofen axetil, piketoprofen-amide, and nepafenac are ester prodrugs that inhibit COX-2. The combination of galangin-like flavonol compounds with these prodrug metabolites may lead to the development of novel COX-2 inhibitors. This review focuses on the most compelling evidence regarding the role and mechanism of COX-2 in cardiovascular diseases and demonstrates that quercetin-like compounds exert potential cardioprotective effects by serving as cofactors of COX-2.

We investigated the binding properties of the (R)- and (S)-enantiomers of the muscarinic antagonists trihexyphenidyl, procyclidine, hexahydro-difenidol, p-fluoro-hexahydro-difenidol, hexbutinol, p-fluoro-hexbutinol, and their corresponding methiodides at muscarinic M1, M2, M3 and M4 receptor subtypes. In addition, binding properties of the (R)- and (S)-enantiomers of oxyphencyclimine were studied. The (R)- enantiomers (eutomers) of all the compounds had a greater affinity than the (S)-isomers for the four muscarinic receptor subtypes. The binding patterns of the (R)- and (S)-enantiomers were generally different. We did not observe any general correlation between the potency of the high-affinity enantiomer and the affinity ratio (eudismic ratio) of the two enantiomers. The results are discussed in terms of a 'four subsites' binding model.

Lisuride Maleate (Dopergin) is semi synthetic ergot alkaloid used for a variety of medical conditions. It is licensed for use in Canada, EU and Middle East countries and is marketed by various drug companies. There are no reported cases of lisuride toxicity in the literature on Google Search or Pub med Search. Herein, we present a case of accidental overdose of lisuride maleate in a 21-month-old Saudi male and further clinical course and management. The aim of this report was to document the unusual features of lisuride toxicity in pediatric patients and to guide physicians for its management.

Currently, there is no specific treatment to cure COVID-19. Many medicinal plants have antiviral, antioxidant, antibacterial, antifungal, anticancer, wound healing etc. Therefore, the aim of the current study was to screen for potent inhibitors of N-terminal domain (NTD) of nucleocapsid phosphoprotein of SARS-CoV-2. The structure of NTD of RNA binding domain of nucleocapsid phosphoprotein of SARS coronavirus 2 was retrieved from the Protein Data Bank (PDB 6VYO) and the structures of 100 different phytocompounds were retrieved from Pubchem. The receptor protein and ligands were prepared using Schrodinger's Protein Preparation Wizard. Molecular docking was done by using the Schrodinger's maestro 12.0 software. Drug likeness and toxicity of active phytocompounds was predicted by using Swiss adme, admetSAR and protox II online servers. Molecular dynamic simulation of the best three protein- ligand complexes (alizarin, aloe-emodin and anthrarufin) was performed to study the interaction

stability. We have identified three potential active sites (named as A, B, C) on receptor protein for efficient binding of the phytocompounds. We found that, among 100 phytocompounds, emodin, aloe-emodin, anthrarufin, alizarine, and dantron of *Rheum emodi* showed good binding affinity at all the three active sites of RNA binding domain of nucleocapsid phosphoprotein of COVID-19.The binding energies of emodin, aloe-emodin, anthrarufin, alizarine, and dantron were -8.299, -8.508, -8.456, -8.441, and -8.322 Kcal mol^{-1} respectively (site A), -7.714, -6.433, -6.354, -6.598, and -6.99 Kcal mol^{-1} respectively (site B), and -8.299, 8.508, 8.538, 8.841, and 8.322 Kcal mol^{-1} respectively (site C). All the active phytocompounds follows the drug likeness properties, non-carcinogenic, and non-toxic. Theses phytocompounds (alone or in combination) could be developed into effective therapy against COVID-19. From MD simulation data, we found that all three complexes of 6VYO with alizarin, aloe-emodin and anthrarufin were stable up to 50 ns. These phytocompounds can be tested further for *in vitro* or *in vivo* and used as a potential drug to cure SARS-CoV-2 infection

Human acid ceramidase (AC) is a lysosomal cysteine amidase, which has received a great deal of interest in recent years as a potential target for the development of new therapeutics against melanoma and glioblastoma tumors. Despite the strong interest in obtaining structural information, only the structures of the apo-AC enzyme in its zymogen and activated conformations are available. In this work, the crystal structure of AC in complex with the covalent carmofur inhibitor is presented. Carmofur is an antineoplastic drug containing an electrophilic carbonyl reactive group that targets the catalytic cysteine. This novel structural data explains the basis of the AC inhibition, provides insights into the enzymatic properties of the protein, and is a great aid toward the structure-based drug design of potent inhibitors for AC, providing the detailed mechanism, which has eluded the scientific community for more than 30 years, of carmofur's mysterious 5-fluorouracil-independent antitumor activity.

This study aimed to evaluate the success of H.pylori eradication therapy in patients with dyspepsia by therapeutics regimes with and without clidinium C.Helicobacter pylori infections are reported in all parts of the world. Appropriate antibiotic therapy can treat infection. The ideal treatment regimen has not been specified.In a randomized, double blind clinical trials study, 250 patients with dyspepsia were enrolled. All patients were treated by Omeprazole, Metronidazole, Amoxicillin and Bismuth (OMAB) for two weeks. One tablet clidinium C before each meal was added to this regimen in the intervention group (A). Urea Breath Test (UBT) was carried out after 8-12 weeks after treatment for evaluation of H.pylori eradication.132 patients in the intervention group (A) and 118 patients in the control group (B) were enrolled to the study. The rate of eradication in group A was significantly higher than group B (62.1% vs. 50%, p=0.04).The results supported the effect of aclidinium C for increasing of helicobacter pylori eradication, but further studies need to be performed.

In the Cardiac Arrhythmia Suppression Trial, designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death, patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The use of encainide and flecainide was discontinued because of excess mortality. We examined the mortality and morbidity after randomization to encainide or flecainide or their respective placebo.

The purpose of the present series of experiments was to measure and compare the effects of an anticholinergic drug (isopropamide) and an antagonist of the histamine H2 receptor (metiamide) on food-stimulated acid secretion. Patients with duodenal ulcers were stimulated by a steak meal, and acid secretion was measured by in vivo intragastric titration. The largest dose of isopropamide that can be taken clinically without producing intolerable side effects (maximum tolerated dose) suppressed food-stimulated acid secretion by 35%. By contrast, metiamide in a 400-mg dose produced no side effects and almost completely abolished food-stimulated acid secretion. A dose-response curve revealed that a 50-mg dose of metiamide was required to suppress food-stimulated acid secretion by 50%. Further studies showed that metiamide and

isopropamide are additive in suppressing food-stimulated acid secretion, and that metiamide has no effect on serum gastrin concentration or on gastric emptying.

ISOFEZOLAC is a non-steroid anti-inflammatory drug, prostaglandin synthetase inhibitor. It is indicated for use in various forms of rheumatoid arthritis and osteoarthritis.

Posaconazole is typically used for preventing invasive yeast and mold infections such as invasive aspergillosis in high-risk immunocompromised patients. The oral suspension was the first released formulation and many pharmacokinetic and pharmacodynamic studies of this formulation have been published. Erratic absorption profiles associated with this formulation were widely reported. Posaconazole exposure was found to be significantly influenced by food and many gastrointestinal conditions, including pH and motility. As a result, low posaconazole plasma concentrations were obtained in large groups of patients. These issues of erratic absorption urged the development of the subsequently marketed delayed-release tablet, which proved to be associated with higher and more stable exposure profiles. Shortly thereafter, an intravenous formulation was released for patients who are not able to take oral formulations.
Both new formulations require a loading dose on day 1 to achieve high posaconazole concentrations more quickly, which was not possible with the oral suspension. So far, there appears to be no evidence of increased toxicity correlated to the higher posaconazole exposure achieved with the regimen for these formulations. The higher systemic availability of posaconazole for the delayed-release tablet and intravenous formulation have resulted in these two formulations being preferable for both prophylaxis and treatment of invasive fungal disease. This review aimed to integrate the current knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, clinical experience in special populations, and new therapeutic strategies in order to get a clear understanding of the clinical use of this drug.

The physicochemical and sunscreen properties of marl as a function of particle size were investigated. The research findings established that the marl under investigation consisted of more than 95% calcium carbonate ($CaCO_3$). The particles of marl inspected under a scanning electron microscope were calcite, which is the stable polymorph of $CaCO_3$, with a rhombohedral structure. The particle size classification by the sieving method showed that grinding using a ball mill could downsize the marl particles by 2 to 3 times, reaching below 15 µm on average. Marl particles showed a tendency to reflect ultraviolet A (UVA) rays rather than UVB rays and a possibility to steadily absorb both UVAII and UVAI. Finer particles obtained after a longer grinding process demonstrated higher efficacy regarding UV reflection and absorption properties. The 3 wt.% marl displayed a sun protection factor (SPF) value of 1 to 2. However, marl demonstrated a good ability to protect against radiation over a broad spectrum range with a critical wavelength above 370 nm. The addition of marl in the formulation containing avobenzone and octinoxate had a positive synergistic effect because the marl was able to increase the UV absorbance efficacy (based on the area under the curve (AUC) value) and SPF value of the cream. Furthermore, it was also discovered that the added marl powder could slow the decrease in UV protection efficacy of the products in terms of the AUC calculated from the absorbance profile after exposure to simulated UV rays with an amplitude range of 10 J/cm^2 to 40 J/cm^2 for 30 min, which was similar to the results obtained from octocrylene and bemotrizinol.

Oxyphenisatin (3,3-bis(4-hydroxyphenyl)-1H-indol-2-one) and several structurally related molecules have been shown to have in vitro and in vivo antiproliferative activity. This study aims to confirm and extend mechanistic studies by focusing on oxyphenisatin acetate (OXY, NSC 59687), the pro-drug of oxyphenisatin. Results confirm that OXY inhibits the growth of the breast cancer cell lines MCF7, T47D, HS578T, and MDA-MB-468. This effect is associated with selective inhibition of translation accompanied by rapid phosphorylation of the nutrient sensing eukaryotic translation initiation factor 2α (eIF2α) kinases, GCN2 and PERK. This effect was paralleled by activation of AMP-activated protein kinase (AMPK) combined with reduced

phosphorylation of the mammalian target of rapamycin (mTOR) substrates p70S6K and 4E-BP1. Microarray analysis highlighted activation of pathways involved in apoptosis induction, autophagy, RNA/protein metabolism, starvation responses, and solute transport. Pathway inhibitor combination studies suggested a role for AMPK/mTOR signaling, de novo transcription and translation, reactive oxygen species (ROS)/glutathione metabolism, calcium homeostasis and plasma membrane Na(+) /K(+) /Ca(2+) transport in activity. Further examination confirmed that OXY treatment was associated with autophagy, mitochondrial dysfunction, and ROS generation. Additionally, treatment was associated with activation of both intrinsic and extrinsic apoptotic pathways. In the estrogen receptor (ER) positive MCF7 and T47D cells, OXY induced TNFα expression and TNFR1 degradation, indicating autocrine receptor-mediated apoptosis in these lines. Lastly, in an MCF7 xenograft model, OXY delivered intraperitoneally inhibited tumor growth, accompanied by phosphorylation of eIF2α and degradation of TNFR1. These data suggest that OXY induces a multifaceted cell starvation response, which ultimately induces programmed cell death.

Amyotrophic lateral sclerosis (ALS) is a progressive, adult onset neurodegenerative disease that is always fatal. The history of ALS drug discovery is fraught with many stops and starts. It took 22 years after the FDA approval of the anti-excitotoxic drug Riluzole before another drug was found to be effective in altering ALS progression: the anti-oxidant Edaravone.

Ultrasound-facilitated catheter-directed thrombolysis is used with low-dose alteplase to treat pulmonary embolism. This reduces the risk of bleeding that accompanies systemic administration of higher alteplase doses. Some studies suggest that alteplase given over 2 to 6 hours is safe and effective, but there are few data to support the stability of alteplase under these conditions. Therefore, we undertook this in vitro study to determine the duration of alteplase stability. Alteplase was prepared in solutions of 8 mg in 100 mL, 6 mg in 150 mL, and 8 mg in 200 mL. Solutions were administered through the EkoSonic Endovascular System (with and without ultrasound) to simulate administration over 2, 4, and 6 hours. Alteplase was assessed with reversed-phase high-performance liquid chromatography (RP-HPLC). Assays were performed at time 0 and at 30-minute intervals during simulated infusion. An enzyme-linked immunosorbent assay was used to measure alteplase concentrations at time 0 and at 15-minute intervals during simulated infusion. By using RP-HPLC in the absence of ultrasound, the alteplase concentration remained within 1% of the original concentration through 120, 240, and 360 minutes of infusion. By using RP-HPLC for measurement, alteplase in the presence of ultrasound degraded steadily over time to ∼90% of its original amount in 120 minutes, ∼80% in 240 minutes, and ∼70% in 360 minutes. The remaining alteplase was available for enzymatic activity. Alteplase solutions of 0.04 and 0.08 mg/mL degraded steadily over time during simulated ultrasound-facilitated catheter-directed administration. Alteplase that did not degrade remained available for enzymatic activity.

The efficacy and safety of nivolumab plus cabozantinib as compared with those of sunitinib in the treatment of previously untreated advanced renal-cell carcinoma are not known. In this phase 3, randomized, open-label trial, we randomly assigned adults with previously untreated clear-cell, advanced renal-cell carcinoma to receive either nivolumab (240 mg every 2 weeks) plus cabozantinib (40 mg once daily) or sunitinib (50 mg once daily for 4 weeks of each 6-week cycle). The primary end point was progression-free survival, as determined by blinded independent central review. Secondary end points included overall survival, objective response as determined by independent review, and safety. Health-related quality of life was an exploratory end point.Overall, 651 patients were assigned to receive nivolumab plus cabozantinib (323 patients) or sunitinib (328 patients). At a median follow-up of 18.1 months for overall survival, the median progression-free survival was 16.6 months (95% confidence interval [CI], 12.5 to 24.9) with nivolumab plus cabozantinib and 8.3 months (95% CI, 7.0 to 9.7) with sunitinib (hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.64; P<0.001). The probability of overall survival at 12 months was 85.7% (95% CI, 81.3 to 89.1) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5 to 80.0) with sunitinib (hazard ratio for

death, 0.60; 98.89% CI, 0.40 to 0.89; P = 0.001). An objective response occurred in 55.7% of the patients receiving nivolumab plus cabozantinib and in 27.1% of those receiving sunitinib (P<0.001). Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups. Adverse events of any cause of grade 3 or higher occurred in 75.3% of the 320 patients receiving nivolumab plus cabozantinib and in 70.6% of the 320 patients receiving sunitinib. Overall, 19.7% of the patients in the combination group discontinued at least one of the trial drugs owing to adverse events, and 5.6% discontinued both. Patients reported better health-related quality of life with nivolumab plus cabozantinib than with sunitinib.Nivolumab plus cabozantinib had significant benefits over sunitinib with respect to progression-free survival, overall survival, and the likelihood of response in patients with previously untreated advanced renal-cell carcinoma.

To provide a drug review of the newly FDA approved catechol-O-methyl transferase (COMT) inhibitor, opicapone, for the use of end-of-motor motor fluctuation in adults with Parkinson's disease. *Data sources*: A literature search of Pubmed was performed till May 2020 using the following key terms: opicapone, Ongentys, and BIA 9-1067. Review articles, clinical trials, and drug monographs were reviewed. *Study selection and data extraction*: Relevant English-language monographs and studies conducted in humans were considered. *Data synthesis*: Opicapone was FDA approved for the treatment of end-of-motor motor fluctuation in adults with Parkinson's disease in April 2020 based on two published randomized clinical trials that were 14 to 15 weeks in duration called BIPARK I and BIPARK II. Based on the clinical trials, 50 mg of opicapone once daily was shown to be noninferior to entacapone and reduced the mean off time by about 50 min when compared to placebo. Most common treatment-emergent adverse events were dyskinesia, falls, insomnia, and elevated blood creatine phosphokinase levels. *Relevance to patient care and clinical practice*: Opicapone overcomes the limitations associated with other COMT inhibitors since it is dosed once daily, well tolerated, and has not been associated with the risk of hepatic failure. When switching from entacapone to opicapone a reduction in "off" time of -39.3 min was also seen. *Conclusions*: Opicapone is a once daily 3rd generation COMT inhibitor that has the potential to benefit patients with Parkinson's disease who are experiencing end-of-motor fluctuations.

Gluconolactone (D-glucono-1,5-lactone or GDL) is a food additive which presents in dietary products such as tofu, yogurt, cheese, bread, wine, etc. GDL has long been considered as a free radical scavenger; however, its role in cardioprotection remains elusive. In this study, using a mouse model of myocardial ischemia/reperfusion (I/R) injury and a model of hypoxia/reoxygenation (H/R) in neonatal rat cardiomyocytes (NRCM), we explored the role of GDL in I/R injury. We found that GDL (5 mg/kg, i.p.) attenuated myocardial I/R injury as evidenced by decreased infarct size, release of cardiac injury markers and apoptosis.
Additionally, GDL decreased reperfusion-induced arrhythmias and oxidative stress. These effects were also observed in parallel *in vitro* studies. Mechanistically, we found that GDL treatment was strongly associated with activation of pro-survival extracellular signal-regulated kinase (ERK) signaling both *in vivo* and *in vitro*, and pharmacological inhibition of ERK signaling *via* U0126 attenuated GDL-induced cardioprotection against H/R injury in NRCM cells. To reveal how GDL regulates ERK signaling, we predicted the putative targets of GDL by Swiss Target Prediction, and protein kinase C (PKC) emerged as the most promising target for GDL. By pharmacological intervention and immunofluorescence, we found that PKCε, an important member of the PKC family, was activated after GDL treatment in heart, thereby leading to ERK activation and cardioprotection against I/R injury. Taken together, our results demonstrated that GDL acts as a potent activator of PKCε and, thus, provides cardioprotection against I/R injury *via* activation of ERK signaling.

The aim of this study was to determine the ability of a disc susceptibility test using faropenem (10 μg) to predict carbapenemase activity in Enterobacteriaceae. A collection of 166 isolates of carbapenemase-producing Enterobacteriaceae (CPE) and 82 isolates of Enterobacteriaceae that produced other β-lactamases was compiled from diverse sources. Disc susceptibility testing was

performed using the CLSI/EUCAST methodology with discs of faropenem (10 μg), temocillin (30 μg), and four carbapenems (each 10 μg). A further prospective evaluation of the faropenem disc susceptibility test was performed using 205 consecutive isolates referred to a United Kingdom reference laboratory in parallel with molecular methods for carbapenemase detection. Of 166 isolates of CPE, 99% showed growth up to the edge of a 10-μg faropenem disc compared with only 6% of other β-lactamase producers (sensitivity, 99%; specificity, 94%). A "double zone" around 10-μg faropenem discs was frequently associated with OXA-48 producers. Of the carbapenems, the most useful agent was imipenem, where a zone diameter of ≤ 23 mm as a predictor of carbapenemase activity had a sensitivity of 99% and a specificity of 85%. The presence of no zone of inhibition around a 30-μg temocillin disc was a consistent feature of strains producing OXA-48 carbapenemase. For 205 isolates of Enterobacteriaceae referred to a United Kingdom reference laboratory, growth up to a 10-μg faropenem disc correctly identified 84 of 86 carbapenemase producers (98% sensitivity), with a specificity of 87%. Disc susceptibility testing using faropenem (10 μg) is a simple, convenient, and highly predictive screening test for carbapenemase-producing Enterobacteriaceae.

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Nomegestrol acetate (NOMAC) 2.5 mg with 17-beta estradiol (E2) 1.5 mg is a new combined oral contraceptive (COC) formulation and is the first monophasic E2 pill to be marketed, having been licensed for use in Europe in 2011. It is available to be taken daily in a regimen of 24 active pills followed by four placebo pills. NOMAC is a highly selective 19-nor progestogen derivative with specific binding to progesterone receptors, anti-estrogenic activity and no androgenic, mineralocorticoid nor glucocorticoid effects. E2 is an estrogen that is identical to endogenous estrogen. While it has been in use for only a short period of time, current evidence suggests that NOMAC/E2 is just as effective, safe, and acceptable as existing COC preparations. Two large Phase III trials conducted in the Americas and across Europe, Australia, and Asia showed lower cumulative pregnancy rates in the NOMAC/E2 groups compared to the drospirenone (DRSP) 3 mg in combination with ethinyl estradiol (EE) 30 μg (DRSP/EE) groups but this difference was not statistically significant. NOMAC/E2 exhibits a good safety profile and has less effects on cardiovascular risk, hemostatic, metabolic, and endocrine factors in comparison to COCs containing EE in combination with levonorgestrel (LNG) or DRSP. NOMAC/E2 has also been found to cause less breast cell proliferation when compared to E2 alone and has some anti-proliferative effect on human breast cancer cells. NOMAC/E2 is considered acceptable as its compliance, continuation rates, and bleeding patterns were similar to COCs containing DRSP/EE and LNG 150 μg combined with EE 30 μg or LNG 100 μg combined with EE 20 μg (LNG/EE). However, discontinuation was found to be slightly higher in the NOMAC/E2 groups

in the two large Phase III trials comparing NOMAC/E2 use with DRSP/EE. As the scientific literature has limited information on NOMAC/E2, further experience with NOMAC/E2 is required.

Findings from previous meta-analyses of randomized clinical trials (RCTs) in premature infants with respiratory distress syndrome (RDS) varied as to whether clinical outcomes differed by type of animal-derived pulmonary surfactant; real-world evidence (RWE) was excluded. We extracted study characteristics and outcomes from full-text articles from a systematic search for studies that compared beractant with poractant alfa for RDS in preterm infants. RWE data were tabulated; RCT data were subjected to meta-analyses. Designs, patient characteristics, and follow-up durations varied widely among studies (4 RWE, 15 RCT). RWE studies with adjusted odds ratios (ORs) found no statistically significant between-treatment differences in outcomes. In RCT meta-analyses, no statistically significant between-treatment differences were observed for death (OR [95% confidence interval], 1.35 [0.98-1.86]), bronchopulmonary dysplasia (1.25 [0.96-1.62]), pneumothorax (1.21 [0.72-2.05]), and air leak syndrome (2.28 [0.82-6.39]). Collectively, outcomes were similar with beractant and poractant alfa in RWE studies and pooled RCTs.

We have investigated the effects of two novel antiparkinsonian drugs, talipexole (Domin) and pramipexole, on MPTP-induced dopamine (DA) reduction in the striatum of C57BL/6N mice in comparison with those of bromocriptine. Fifteen days after MPTP treatment (25 mg/kg, i.p., given daily for 5 days), the DA content in the striatum was decreased to 40-60% of the control value. Among the three dopamine receptor agonists, talipexole and pramipexole (1 mg/kg, i.p., once a day for 20 days) more significantly suppressed the MPTP-induced DA reduction in the striatum than bromocriptine (10 mg/kg, i.p., once a day for 20 days). Talipexole did not influence [3H]MPP+ uptake into striatal synaptosomes. These results suggest that talipexole and pramipexole have a protective effect against MPTP-induced DA reduction in the striatum of C57BL/6N mice.

The prognosis of adult acute myeloid leukemia (AML) remains poor, with the long-term survival rate less than 50%. However, the current paradigms of treatment are changing through a better understanding of the disease genetics and pathophysiology. Since 2017, eight new drugs have been approved by the U.S. Food and Drug Administration for the treatment of AML, including the FLT3 inhibitors midostaurin and gilteritinib, the IDH inhibitors ivosidenib and enasidenib, the anti-CD33 monoclonal antibody gemtuzumab ozogamicin, liposomal daunorubicin and cytarabine, the hedgehog pathway inhibitor glasdegib and the BCL-2 inhibitor venetoclax. Preclinical data demonstrated the anti-leukemic efficacy of venetoclax in AML and its synergy when combined with hypomethylating agents or chemotherapy agents. Clinical trials have demonstrated the clinical benefit of venetoclax-based therapies in newly diagnosed AML, leading to the recent FDA approval of venetoclax in combination with hypomethylating agents or low-dose cytarabine for older adults with newly diagnosed AML. Herein, we focus on the role of single-agent BCL-2 inhibition in AML and review the clinical studies of venetoclax-based combination regimens and the evolving mechanisms of resistance.

Circulating factor XIII (FXIII) consists of two active (A) and two carrier (B) subunits in tetrameric form. Congenital FXIII deficiency is a rare autosomal-recessive trait that mostly results from an FXIII A-subunit deficiency. Classic coagulation assays, such as prothrombin time or activated partial thromboplastin time, are not sensitive to FXIII; therefore, specific FXIII assays are necessary to detect the deficiency. The clinical picture of congenital FXIII deficiency comprises abortions, umbilical cord bleeding, increased surgical bleeding, intracerebral hemorrhage (which can, unfortunately, be the very first sign of severe FXIII deficiency), menorrhagia, and wound-healing disorders. Given the risk of intracranial hemorrhage, continued prophylaxis is to be recommended in severe deficiency, even in the actual absence of bleeding symptoms. Functional FXIII half-life decreases in consumptive processes (eg, surgery), explaining why increased dosing is needed in such situations. A recombinant FXIII (rFXIII)

subunit-A molecule, which is expressed in Saccharomyces cerevisiae, has been evaluated for replacement therapy in congenital FXIII deficiency. The bleeding frequency under continued rFXIII prophylaxis during a year-long treatment period was significantly lower compared to on-demand treatment. Importantly, no severe spontaneous bleedings occurred, and bleeding requiring additional intervention only occurred after relevant trauma. Treatment with rFXIII proved to be safe: antibodies against rFXIII detected in four patients were not considered clinically relevant. No allergic reactions were observed. These data show that rFXIII can be used safely and effectively for continued prophylaxis in congenital FXIII deficiency; it is conceivable that this also holds true for treatment of acute bleeding, but clinical proof of this is pending.

Inhalation of the enzyme dornase alfa reduces sputum viscosity and improves clinical outcomes of people with cystic fibrosis. This is an update of a previously published Cochrane Review. determine whether the timing of dornase alfa inhalation (in relation to airway clearance techniques or morning versus evening inhalation) has an impact on objective and subjective measures of clinical efficacy in people with cystic fibrosis.Relevant randomised and quasi-randomised controlled trials were identified from the Cochrane Cystic Fibrosis Trials Register, Physiotherapy Evidence Database (PEDro), clinical trial registries and international cystic fibrosis conference proceedings.Date of the most recent search: 06 June 2018. Any trial of dornase alfa in people with cystic fibrosis where timing of inhalation was the randomised element in the trial with either: inhalation before compared to after airway clearance techniques; or morning compared to evening inhalation. Both authors independently selected trials, assessed risk of bias and extracted data with disagreements resolved by discussion. Relevant data were extracted and, where possible, meta-analysed.

Fear of withdrawal symptoms has been cited by survey respondents as the main reason that they continued to use opioids. Lofexidine is an α2-adrenergic agonist that decreases the sympathetic outflow that results in the characteristic symptoms of opioid withdrawal. A structural analog of clonidine, lofexidine has a higher affinity and specificity for the α2a receptors and does not reinforce opioid dependence. Withdrawal symptoms correlate approximately to the half-life of the opioid; patient factors such as age, duration of opioid exposure, physical status, and other considerations may influence the nature and duration of withdrawal symptoms. For patients with opioid use disorder and psychiatric comorbidities, withdrawal may be destabilizing and may exacerbate mental health status. Lofexidine has been shown in clinical trials to be safe and effective in helping to manage the symptoms of withdrawal and has been recommended in guidelines for this purpose. Adverse events associated with lofexidine include QT prolongation, hypotension, orthostasis, and bradycardia. The maximum course of treatment is 14 days, and doses should be titrated, with the recommended maximum dose to coincide with the most severe withdrawal symptoms

A non-randomised, phase 2 study showed activity and tolerability of eribulin in advanced or metastatic soft-tissue sarcoma. In this phase 3 study, we aimed to compare overall survival in patients with advanced or metastatic soft-tissue sarcoma who received eribulin with that in patients who received dacarbazine

Pegaspargase (Oncaspar®), a pegylated form of native Escherichia coli-derived L-asparaginase (hereafter referred as E. coliL-asparaginase), is indicated in the USA and EU for the treatment of acute lymphoblastic leukaemia (ALL) as a component of multi-agent chemotherapy in paediatric and adult patients. Relative to E. coliL-asparaginase, pegaspargase has a prolonged circulation time, thereby offering less frequent administration. Moreover, pegylation of E. coliL-asparaginase may diminish the immunogenicity of the enzyme. Based on extensive evidence, intramuscular (IM) or intravenous (IV) administration of pegaspargase as a component of a multi-agent chemotherapy is an effective first-line treatment for paediatric and adult patients with ALL, as well as for the treatment of paediatric and adult patients with ALL and hypersensitivity to E. coliL-asparaginase. Pegaspargase had a manageable tolerability profile in paediatric and adult patients with newly diagnosed ALL, with the most commonly occurring

adverse events being generally consistent to that seen with E. coliL-asparaginase. Pegaspargase treatment in patients with relapsed ALL and hypersensitivity to E. coliL-asparaginase had a similar tolerability profile to that observed in patients with newly diagnosed ALL. Given the potentially reduced immunogenicity and more convenient dosage regimen over E. coliL-asparaginase, pegaspargase remains an important and effective treatment option for paediatric and adult patients with ALL, including those with hypersensitivity to E. coliL-asparaginase

Oxetorone (INN), as **oxetorone fumarate** (USAN) (brand names **Nocertone**, **Oxedix**), is a serotonin antagonist, antihistamine, and alpha blocker used as an antimigraine drug. Association with hyperprolactinemia has been described[5] and antidopaminergic actions are also suspected

Quingestanol acetate is a progestin, or a synthetic progestogen, and hence is an agonist of the progesterone receptor, the biological target of progestogens like progesterone.[2][3][4] It has weak androgenic and estrogenic activity and no other important hormonal activity.[2][3][4] The medication is a prodrug of norethisterone in the body, with quingestanol and norethisterone acetate occurring as intermediates

Floctafenine, a hydroxyquinoline derivative with analgesic properties, is widely used in Thailand and many other countries. The objectives of this study were to evaluate in Thai healthy volunteers: i) the inhibition of whole blood cyclooxygenase(COX)-2 and COX-1 activity by floctafenine and its metabolite floctafenic acid in vitro and ex vivo after dosing with floctafenine; ii) the possible interference of floctafenine administration with aspirin antiplatelet effects. We performed an open-label, cross-over, 3-period study, on 11 healthy Thai volunteers, who received consecutively floctafenine(200mg/TID), low-dose aspirin(81mg/daily) or their combination for 4 days, separated by washout periods. Floctafenine and floctafenic acid resulted potent inhibitors of COX-1 and COX-2 in vitro (floctafenic acid was more potent than floctafenine) showing a slight preference for COX-1. After dosing with floctafenine alone, whole blood COX-1 and COX-2 activities were inhibited ex vivo in a time-dependent fashion which paralleled floctafenic acid plasma concentrations. Aspirin alone inhibited profoundly and persistently platelet COX-1 activity and AA-induced platelet aggregation throughout 24-h dosing interval which was affected by the co-administration of floctafenine. At 24 h after dosing with aspirin and floctafenine, the inhibition of platelet thromboxane(TX)B2 generation and aggregation were significantly(P less than 0.05) lower than that caused by aspirin alone.
Therapeutic dosing with floctafenine profoundly inhibited prostanoid biosynthesis through the rapid conversion to floctafenic acid. Floctafenine interfered with the antiplatelet effect of aspirin. Our results suggest that floctafenine should be avoided in patients with cardiovascular disease under treatment with low-dose aspirin.

Racecadotril is a guideline-recommended option for the treatment of acute diarrhea in children but existing guidelines and previous reviews of the field are based on a small fraction of published evidence. Therefore, we have performed a systematic search for randomized controlled trials evaluating racecadotril as add-on or in comparison to other treatments

Fasudil is an inhibitor of Rhoa/ROCK signaling, which is involved in anti-inflammatory and anti-injury effects. The purpose of this study was to explore the effects of Fasudil on acetaminophen (APAP)-induced liver injury and reveal its potential molecular mechanism. In this study, C57BL/6 J mice were divided into different groups and treated with APAP and specified dose of Fasudil. HE staining was used to detect the changes of liver pathological tissues induced by APAP. ELISA assay was performed to detected the level of related factors. Western blot was used to detect the expressions of Rhoa, ROCK1, ROCK2. CD86 and CD6 were determined by RT-PCR and immunohistochemical staining detected the difference in CD86 expression. Rhoa/ROCK expression was increased in APAP-induced liver injury, and Fasudil targeted the expression of Rhoa/ROCK. Fasudil inhibits APAP-induced hepatic pathological changes and liver function injury. Fasudil inhibits the release of APAP-induced

systemic inflammatory factors in liver tissue. Fasudil inhibits the activity of antioxidant enzymes, lipid peroxidation and macrophage infiltration induced by APAP in liver tissues. Fasudil alleviates APAP-induced liver injury via targeting Rhoa/ROCK signal pathway, indicating the possibility for clinical use of Fasudil in APAP-induced liver injury.

lefacept is a bioengineered fusion protein of soluble lymphocyte function antigen (LFA-3) with Fc fragments of IgG1. It is marketed in many countries for the treatment of moderate to severe psoriasis. This paper reviews the data supporting the use of alefacept in psoriasis and psoriatic arthritis.

Nafamostat mesylate, an apparent soi-disant panacea of sorts, is widely used to anticoagulate patients undergoing hemodialysis or cardiopulmonary bypass, mitigate the inflammatory response in patients diagnosed with acute pancreatitis, and reverse the coagulopathy of patients experiencing the commonly preterminal disseminated intravascular coagulation in the Far East. The serine protease inhibitor nafamostat mesylate exhibits significant neuroprotective effects in the setting of neurovascular ischemia. Nafamostat mesylate generates neuroprotective effects by attenuating the enzymatic activity of serine proteases, neuroinflammatory signaling cascades, and the endoplasmic reticulum stress responses, downregulating excitotoxic transient receptor membrane channel subfamily 7 cationic currents, modulating the activity of intracellular signal transduction pathways, and supporting neuronal survival (brain-derived neurotrophic factor/TrkB/ERK1/2/CREB, nuclear factor kappa B. The effects collectively reduce neuronal necrosis and apoptosis and prevent ischemia mediated disruption of blood-brain barrier microarchitecture. Investigational clinical applications of these compounds may mitigate ischemic reperfusion injury in patients undergoing cardiac, hepatic, renal, or intestinal transplant, preventing allograft rejection, and treating solid organ malignancies. Neuroprotective effects mediated by nafamostat mesylate support the wise conduct of randomized prospective controlled trials in Western countries to evaluate the clinical utility of this compound

Triple antimalarial combination therapies combine potent and rapidly cleared artemisinins or related synthetic ozonides, such as arterolane, with two, more slowly eliminated partner drugs to reduce the risk of resistance. We aimed to assess the safety, tolerability, and efficacy of arterolane-piperaquine-mefloquine versus arterolane-piperaquine and artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in Kenyan children.

Flunoxaprofen (FLX) is a chiral nonsteroidal anti-inflammatory drug that was withdrawn from clinical use because of concerns of potential hepatotoxicity. FLX undergoes highly stereoselective chiral inversion mediated through the FLX-S-acyl-CoA thioester (FLX-CoA) in favor of the (R)-(-)-isomer. Acyl-CoA thioester derivatives of acidic drugs are chemically reactive species that are known to transacylate protein nucleophiles and glutathione (GSH). In this study, we investigated the relationship between the stereoselective metabolism of (R)-(-)- and (S)-(+)-FLX to FLX-CoA and the subsequent transacylation of GSH forming FLX-S-acyl-glutathione (FLX-SG) in incubations with rat hepatocytes in suspension. Thus, when hepatocytes (2 million cells/ml) were treated with (R)-(-)- or (S)-(+)-FLX (100 microM), both FLX-CoA and FLX-SG were detected by sensitive liquid chromatography-tandem mass spectrometry techniques. However, these derivatives were observed primarily from (R)-(-)-FLX incubation extracts, for which the formation rates of FLX-CoA and FLX-SG were rapid, reaching maximum concentrations of 42 and 2.8 nM, respectively, after 6 min of incubation. Incubations with (S)-(+)-FLX over 60 min displayed 8.1 and 2.7% as much FLX-CoA and FLX-SG area under the concentration versus time curves, respectively, compared with corresponding incubations with (R)-(-)-FLX. Coincubation of lauric acid (1000 microM) with (R)-(-)-FLX (10 microM) led to the complete inhibition of FLX-CoA formation and a 98% inhibition of FLX-SG formation.
Reaction of authentic (R,S)-FLX-CoA (2 microM) with GSH (10 mM) in buffer (pH 7.4, 37 degrees C) showed the quantitative formation of FLX-SG after 3 h of incubation. Together, these results demonstrate the stereoselective transacylation of GSH in hepatocyte incubations

containing (R)-(-)-FLX, which is consistent with bioactivation by stereoselective (R)-FLX-CoA formation.

Dandruff is a common condition, affecting up to half the global population of immunocompetent adults at some time during their lives and it has been highly correlated with the over-expression of the fungus Malassezia spp. Climbazole (CBZ) is used as an antifungal and preservative agent in many marketed formulations for the treatment of dandruff. While the efficacy of CBZ in vitro and in vivo has previously been reported, limited information has been published about the uptake and deposition of CBZ in the skin. Hence, our aim was to investigate the skin permeation of CBZ as well as the influence of various solvents on CBZ skin delivery. Four solvents were selected for the permeability studies of CBZ, namely propylene glycol (PG), octyl salicylate (OSal), Transcutol® P (TC) and polyethylene glycol 200 (PEG). The criteria for selection were based on their wide use as excipients in commercial formulations, their potential to act as skin penetration enhancers and their favourable safety profiles. 1% (w/v) solutions of CBZ were applied under infinite and finite dose conditions using Franz type diffusion cells to human and porcine skin. In line with the topical use of CBZ as an antidandruff agent, comparatively low amounts of CBZ penetrated across the skin barrier (<1% of the applied dose of CBZ). Finite dose studies resulted in a higher extraction of CBZ from human skin compared with infinite dose studies ($p < 0.05$). CBZ was also taken up to a higher extent in porcine skin (>7-fold) compared with human skin ($p < 0.05$). Nevertheless, no statistical differences were observed in the amounts that permeated across the different membranes. These preliminary results confirm the potential of simple formulations of CBZ to target the outer layers of the epidermis. The PG and OSal formulations appear to be promising vehicles for CBZ in terms of overall skin extraction and penetration. Future work will expand the range of vehicles studied and explore the reasons underlying the retention of CBZ in the outer layers of the skin.