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Adverse Reactions and Gastrointestinal Tract

A. Lorenzo Hernández[1], E. Ramirez.[1]
and Jf. Sánchez Muñoz-Torrero[2]
[1]*University Autonoma of Madrid*
[2]*University of Extremadura*
Spain

1. Introduction

Adverse drug reactions are common and there is an increasing interest in recognizing them. There are several studies that try to identify epidemiology, true incidence in hospitalized and not hospitalized patients and the main concerns about their causes and possible solutions. Gastrointestinal tract, mainly haemorrhages and peptic disease are the most common site of adverse drug reactions; that´s the reason why we should recognize this problem and how to manage. Also we try to review the most common drugs affecting gastrointestinal tract. Less common and, usually less severe, liver disease and pancreatitis can be produced by adverse drug reactions. In this chapter we review theses aspects of adverse drug events, particularly, those related to drugs affecting gastrointestinal tract.

2. Definition of adverse drug reactions

An adverse drug event is an unwanted and unintended medical event related to the use of medications. An adverse drug event is considered an adverse drug reaction (ADR) when there is a causal link between the event and use of the drug. An adverse drug reaction is considered serious when the patients outcome is one of the following: death, life-threatening, hospitalization (initial or prolonged), disability –significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure or physical activities or quality of life, congenital anomaly or require intervention to prevent permanent impairment or damage [Supplementary information in Appendix 1].

Causality assessment is necessary to determine the likehood that a drug caused a suspected ADR. There are a number of different methods used to judge causation, the first attempts were proposed by Karch and Lasagna (1977), Lecenthal et al. (1979) and Naranjo et a.l (1981). Most of these approaches to assigning causality are based on the following clinical features: temporal relationship between drug exposure and the onset of adverse drug event, characteristic symptoms and laboratory abnormalities and/or histology, and challenge-dechallenge-rechallenge (improvement after stopping the suspected drug and reappearance after starting the agent in question).

ADRs can be considered "on-target" effects, if they are result of exaggerated pharmacology that may be managed by dose reduction or other therapeutic modifications, i.e. hypoglycemia associated with antidiabetic agents. "Off-target" toxicities are frequently more problematic because they may not be predicted from pharmacology and toxicology studies, and they may occur only after prolonged exposure, i.e. hypersensibility reactions associated to antiepileptics. Unexpected ADRs that first appear after marketing authorization of the medication continue trouble clinicians, regulators, and drug sponsors. The most notably cause is the use by large number of patients, providing sufficient statistical power to detect rare events. Other factors include use in special populations, drug inte ractions, renal and hepatic insufficiency, long duration of use and drug withdrawal.

3. Epidemiology of adverse drug reactions

Adverse drug reactions (ADRs) are considered to be among the leading causes of morbidity and mortality. Around 5-25% of hospitals admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience serious ADRs (SADRs) causing significant prolongation of hospital stay and projected that adverse drug events are the fourth to sixth leading cause of death in the United States. Most studies are focused on rates of serious and fatal events in hospitalized patients, probably because tracking of ADRs is more established in the inpatients setting. An English study (Kane-Gill, 2010) found an increase in hospitalizations caused by ADR in about 76.8% in ten years. A recent study of administrative health-care data found an annual ADR prevalence rate of 0.5% among ambulatory-care patients; however, the authors acknowledge this is probably an underestimate of true ADR rates. Ambulatory-care patients experiencing an ADR were younger on average than hospitalized patients.

Risk factors of suffering adverse drug events are: women, elderly and polipharmacy mainly. Women were more likely than men to have ADRs in both outpatients and inpatients settings. In the study from Zopf (2008), the OR of women from suffering ADR was 1.562; (95% CI 0.785, 2.013). Other risk factors implicated in adverse drug reactions are elderly, drug-drug interactions, polipharmacy and renal insufficiency. In the study of Sanchez Muñoz (2011), also drug-drug interactions were as important as age and renal insufficiency in producing adverse drug reactions.

Patients affected by adverse dug events are admitted in internal medicine department and geriatrics quite often, but patients hospitalized in Intensive care units and pediatrics also suffer from these problems.

4. Severity of adverse drug reactions – Fatal adverse drug reaction

It has been estimated than fatal ADRs are expected in approximately 0.32% of hospitalized patients, and complications from drug therapy are the most common adverse event in hospitalized patients. If true, then ADRs are the 4th leading cause of death—ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths. However, some studies show greater severity prevalence and fatality rate. In the hospital setting the study from Kaurr, (Kaurr,2011) observed grade severe of adverse reaction in 13.4% patients. In the study from Sánchez Muñoz-Torrero (2010) the reactions were severe in 17% and fatal in 1.6% of hospitalized patients.

These statistics do not include the number of ADRs that occur in ambulatory settings. The exact number of ADRs is not certain and is limited by methodological considerations. However, whatever the true number is, ADRs represent a significant public health problem. In a Sweden study there were reviewed the death reports in one year in relation with adverse drugs reactions. They found 3.1% of deaths associated with fatal adverse drug events, mostly haemorraghes. 89% of patients died at hospital meanwhile only 35% of patients dead at hospital with no relation with drug events.

So most of studies trying to establish epidemiology and cost of adverse drug reactions demonstrate that these events are harmful and we have to make great efforts to diminish the incidence and morbidity.

5. Cost of adverse drug reactions

In western countries, drug-related illnesses account 5% to 10% of inhospital costs, and being associated with a substantial increase in morbidity and mortality. In addition to their impact on human health, ADRs also have significant impact on healthcare costs. These costs are essentially hospital costs, in particular arising from an increase in length of stay caused by an ADR. Although has been estimated that the occurrence of an ADR during hospitalization or leading to hospitalization is responsible in U.S.A. (data from 1997) for a cost of approximately 2800 Euros in an additional length of stay of 2.2 days, several studies have also pointed out that the structure of ADR cost is heterogeneous, a factor which must be taken into account when developing preventive strategies. Although data of costs were not calculated, Sanchez Muñoz-Torrero et al (2010) study found an increase in hospital staying in almost 9 days (18±17 days vs 9.6±5.8, $p<0.001$), which accounts for more direct and indirect costs of the hospitalization. Also another Spanish (Carrasco Garrido et al, 2010) study found an increase in 19% of hospital costs associated with the appearance of adverse drug events.

6. Potential causes implicated in adverse drug reactions

Older patients are particularly vulnerable to drug-related illness because they are usually on multiple drug regimens, which expose them to the risk of drug interactions (Mallet et al, 2007), and because age is associated with changes in pharmacokinetics and pharmacodinamics (Aronson, 2007).

Onder et al. (2010) developed and validated a risk stratification model (The GerontoNet ADR Risk Score) to identify patients 65 years or older who are at risk for an ADR during hospitalization. They used data from the Italian Group of Pharmacoepidemiology in the Elderly to develop an ADR risk score. The ADR risk score was then validated in a sample of older adults who were admitted to 4 university hospitals in Europe. The number of drugs and history of an ADR were the strongest predictors of ADRs, followed by heart failure, liver disease, presence of 4 or more conditions, and renal failure (Table 1).

Recently Sánchez Muñoz-Torrero et al found that renal function and drug–drug interactions were statistically significant associated with the appearance of ADR. Also duration of hospitalization was associated but it wasn't possible to establish that if duration of hospitalization was the cause or the consequence of ADR. Recently Hamilton et al (2011) reviewed the adverse drug reactions in older people with potentially inappropriate prescriptions.

Variable	OR (95% CI)	Points
≥4 Comorbid conditions	1.31 (1.04-1.64)	1
Heart failure	1.79 (1.39-2.30)	1
Liver disease	1.36 (10.6-1.74)	1
No. of drugs		
≤ 5	1 [Reference]	0
5-7	1.90 (1.35-2.68)	1
≥8	4.07 (2.93-5.65)	4
Previous ADR	2.41 (1.79-3.23)	2
Renal failure	1.21 (0.96-1.51=	1

Abbreviations: ADR, adverse drug reactions; CI, confidence interval; OR, odd ratio.

Table 1. Variables included in the Score (adapted from Onder *et al*)

7. Main drugs implicated in reactions

Drug classes most frequently associated with ADRs in both inpatients and outpatient populations are non steroidal anti-inflamatory drugs (NSAIDs), diuretic, anticoagulants, antiobiotics and antineoplastic agents.

Antibiotic and vaccination reactions are more frequent in the 0 –to-9 year age group.

In adults and elderly people, there a great variety of drugs causing adverse drug reactions. However, it depends the type of hospitalization, the deparment, etc, the type of adverse reactions and drugs implicated are quite different. Pimohamed et al. (2004) found that aspirin was the casual agent in 18% of cases of all admission for ADRs, while other NSAIDs and diuretics were implicates in 12% and 27% respectively. The most common ADRs of NSAIDs were GI bleeding, peptic ulcerations, haemorrhagic cerebrovascular accident, renal impairment, wheezing and rash. Grenouillet-Delacre et al. (2007) found that psychotropic drugs, immunosuppressive drugs, anticoagulants and antibiotics were more than 50% of life-threatening adverse drug reactions at admission to medical intensive care. In Spain, antibiotic and anticoagulants are the drugs more frequently implicated in ADRs appeared during hospitalization but in another epidemiologic study (Carrasco Garrido, 2010) found that main drugs implicated in admission into the hospital were antineoplastics and immunosuppressive therapy. However there are very few studies that show antineoplastics and immunosuppressive therapies as the cause of adverse drug reactions although they are being increasingly used and promote the appearance of infections, medullar aplasia, etc. Also cardiovascular drugs, mainly diuretics and hypotensors drugs account for some common ADRs.

8. Drugs reactions affecting gastrointestinal tract

ADR that cause damage in gastrointestinal tract usually produce GI bleeding/peptic ulcerations, diarrhea (mainly associated to antibiotics), pancreatitis and liver toxicity. About 40% of ADR affect gastrointestinal and liver in hospitalized patients. As said before, gastrointestinal bleeding is the most frequent ADRs causing hospitalization or produced

during hospitalization. In this issue, we try to review the ADRs affecting gastrointestinal tract.

8.1 GI bleeding

Mainly non steroidal anti-inflammatory drugs and antiplatelet/anticoagulants are implicated in gastrointestinal bleeding. The most frequent lesion is gastric erosions (about 40.2%), combination of gastric ulcer and gastric erosions (16.1%), gastric ulcer (15.0%), duodenal ulcer (13.8%), normal (13.8%) and duodenal erosions (1.1%). In a recent study 26% of patients admitted because of gastrointestinal bleeding had antiplatelet or anticoagulants as the cause of bleeding. The distribution of lesions was quite similar to the study from Devy, being gastric ulcer the most common lesion involved in the bleeding. Inhibition of cyclooxygenase, leading to inhibition of gastric prostaglandin synthesis, and impaired GI defense mechanisms represent additional mechanisms of drug-induced GI bleeding. In the particular setting of Intensive Care Units (ICUs) the most frequent lesion found in patients is the stress-related mucosal bleeding, in which another causes apart from drugs are implicated. In the study from Wikman-Jorgensen (2011) mortality of upper gastrointestinal bleeding was 3,5%, all in patients with great comorbidity which limited treatment of bleeding.

Drugs most frequently causing bleeding were aspirin in 36%, acenocumarol in 27%, clopidogrel in 18%. Combination of aspirin and clopidogrel are responsible of 6% of upper gastrointestinal bleeding. Aspirin is the drug more frequently implicated but it may chance in the future because of the increasing use of doble antiplatelet treatments and new anticoagulants (Rivaroxaban, Apixaban and Dabigatran). It is possible than in the near future we begin to see hemorrhages with dabigatran because of the recent approval in USA for the use of treatment in atrial fibrillation, including patients with low risk of thromboembolism. The risk of bleeding is bigger with Rivaroxaban as shown in the prophylaxis studies, but the approval for AF is pending.

Also lower gastrointestinal bleeding is increasing because of use of AINES mainly. New techniques for diagnosing lesions in small and large intestine are proving this increase in lower gastrointestinal bleeding. AINES can cause diverticulum perforation, mucosal inflammation, ulceration, causing bleeding in the intestine. Use of aspirin, clopidogrel or anticoagulants and the lower intestinal bleeding is an issue that has to be studied because of its frequency, use and potential harmful in small and large intestine. There´s little information about its presentation and management.

8.2 Diarrhea

Diarrhoea may be defined by frequency or grams of loose grames per day: 3–5 times per day and/or loose stools 200– 300 grams/day (250 mL/day).

It´s estimated that diarrhoea accounts for the 7% of ADRs. There are lot of drugs producing diarrhea as a secondary effect: metformin, some chemotherapies, antibiotics, mainly clavulanic, clindamicin, immunosuppressant… Most of them cause diarrhea only while taking, or only at the beginning of prescription, but some are associated with chronic diarrhoea as metformin. However, the possibility of a drug causing a severe diarrhea is less common except in the case of antibiotics, hipomotility drugs, steroids, proton pump inhibitors because of the possibility of Clostridium difficile diarrhea.

Mechanisms of drugs producing diarrhoea are multiple: osmotic, secretory, motor, exudative, malabsorptive, infectious/inflammatory, and others. Examples of osmotic diarrhoea are enteral nutrition feeding, magnesium salts, etc. Examples of secretory diarrhoea (increase in intestinal ion secretion or diminution in intestinal ion absorption) are digoxin, quinidine, propafenone and theophiline. Examples or rapid intestinal transit are procinetic and macrolids. Exudative diarrhoea (changes in permeability and integrity of intestinal mucosa) are NSAIDs and antineoplastic. Drug-related malabsorption of fats, carbohydrates, and/or bile can also lead to diarrhea. Examples include octreotide (at high doses), highly active antiretroviral therapy, tetracycline, NSAIDs, and antineoplastic agents. Drug-induced infectious/inflammatory diarrhea includes microbial proliferation, pseudomembranous colitis, and histologic colitis. The risk of antibiotic associated diarrhea is higher with broad-spectrum agents (particularly those with antianaerobic activity and activity against Enterobacteriaceae), agents with high luminal concentrations (although oral/enteral administration is not necessarily a risk), longer duration of therapy, and use of multiple antibiotics.

8.3 Constipation and hypomotility

Anticholinergic drugs are responsible of constipation as well as other adverse reactions in patients, particularly elderly patients. Also opioids prescribed for cancer patients, chronic pain, etc are responsible of constipation which can produce paralitic ileum. In the setting of ICU patients hipomotility and constipation appears in 50-80 % of patients, particularly those with mechanically ventilated.

8.3.1 Hypomotility

Hypomotility is produced mainly abnormalities in propulsive motility, disturbances in esophageal and gastric motility, reduction in lower esophageal sphincter pressure. Exogenous cathecolamines can reduce antral contractions and small bowel peristalsis and alter motility patterns. Opioids inhibit neurotransmitters release and altering water and electrolyte absorption.

8.3.2 Constipation

Constipation is produced by changes in neuronal or motor function in the intestine. The most common cause is opioids. They inhibit the release of acetylcholine from the myenteric plexus and promote in the opioid receptors in the intestine a decreased motility and increase in intestinal fluid absorption. Other drugs implicated in constipation are antihistamines, calcium channel blockers, diuretics, tricyclic antidepressants.

8.4 Pancreatitis

Drug induced pancreatitis accounts for 0.1-2% of pancreatitis. Between 1968 and 1993 a total of 525 different drugs from many different substance classes have been reported to the WHO because they were suspected to induce pancreatitis as an unwanted side effect, The three drugs that are responsible of more cases of pancreatitis are mesalazine, azathioprine and simvastatine. Previously recognized patients with more risk of pancreatitis are pediatric and elderly patients, women, advanced HIV disease and inflammatory bowel disease. The

interesant review from Balani (2008) showed a table with drugs commonly implicated in pancreatitis: ACE inhibitors, ARA-2, loop diuretics and thiazides, statins, bezafibrate, some antibiotics, pentamidine, azathioprine, mercaptopurine, aminosalicylates, anticonvulsivants and antipsychotics, estrogens, carbimazole, some antineoplastics, codeine, sulindac.

In critically ill patients there's also a review of drugs implicated in pancreatitis (Lat, 2010):

8.4.1 Drugs with a likely association

Drugs with a likely association: Asparaginase, azathioprine, cimetidine, corticosteriopids, corticotrophin, cytarabin, dapsone, didanosine, enalapril, estrogens, furosemide, isonizid, mercaptopurine, mesalamine, methyldope, metronidazole, omeprazol, opiates, pentamidine, pravastatin, salycilates, simvastatin, sulfasalizine, sulfamethoxazole/trimethoprim, sulindac, tetracycline, valproic acid.

8.4.2 Drugs with a potential or questionable association

Drugs with a potential or questionable association: acetaminophen, amiodarone, ampicilin, benzapril, carbamazepine, captopril, ceftriaxone, clarithromycin, cyclosporine, diphenoxylate, cisplatinerythromycin, fluvastatin, gemfibrozil, interferon, ribavirin, ketoprofen, lisinopril, ketoprofen, lisinopril, lovastatin, metformin, naproxen, thiazides, octerotide, penicillin, procainamide, propofol, propoxyphene, ramipril, ranitidine, rifampin.

8.5 Drug-Induced Liver Injury (DILI)

Hepatotoxicity and drug-induced liver injury (DILI) are terms used interchangeably. DILI can be defined as a liver injury induced by a drug or herbal medicines leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other competing etiologies. Most cases of DILI are due to idiosyncratic or unexpected reactions. In contrast to paracetamol-induced hepatotoxicity, which occurs with dose-dependent overdose of the drug. Idiosyncratic drug reactions have been traditionally considered dose independent. However, drugs with well-documented idiosyncratic DILI have been shown to have a dose-dependent component. Idiosyncratic DILI, excluding injury caused by acetaminophen overdose, accounts for 7–15% of the cases of acute liver failure in Europe and the United States and is the most frequent reason for the withdrawal of an approved drug from the market. Estimates of the rate of incidence of DILI leading to hospital referral vary from 2.4 per 100,000 person-years (in a retrospective population-based study of 1.64 million UK subjects) to 13.9 per 100,000 inhabitants (in a prospective analysis in France). Complementary or alternative medicines are used by at least 20% of individuals in Western, Eastern, and African cultures, and reports of DILI have increased. Given its rarity, DILI may not be identified during clinical trials and may come to light only after the culprit drug has obtained market approval and large numbers of patients have been exposed. In addition, in preregistration clinical trials, mild asymptomatic liver injuries, often characterized by asymptomatic elevations in liver enzymes, are commonly seen. However, drugs capable of inducing severe DILI as well as drugs that have a low potential for causing severe injury (e.g., aspirin and heparin) can generate similar patterns of liver injury. It is therefore necessary to develop an approach that can distinguish drugs that are likely to cause severe DILI from drugs that are unlikely to do so.

RUCAM algorithm (Roussel Uclaf Causality Assessment Method) was the first algorithm developed specifically for DILI. After the meeting sponsored by the CIOMS (Paris, 1989), with the support of Russel Uclaf pharmaceutical company, the terminology and diagnosis criteria for causality assessment was proposed. The algorithm was validated using external cases with positive rechallenge (49 cases) and 28 controls (patients with acute liver damage not related to drugs) with available information before occurrence of re-exposure, with results of high sensitivity (86%), specificity (89%), positive predictive value (93%) and negative predictive value (78%) [Algorithm RUCAM are showed in Table 1 and 2 of Appendix 2].

International DILI Expert Working Group of clinicians and scientists reviewed current DILI terminology and diagnostic criteria so as to develop more uniform criteria that could be define and characterize the spectrum of clinician syndromes that constitute DILI. In Appendix 2 of supplementary information you will find threshold criteria for definition of a case as being DILI (Box 1), the pattern of liver injury (Box 2), severity (Box 3), causality assessment (Box 4), and chronicity (Box 5). Consensus was also reached on approaches to characterizing DILI in the setting of chronic liver diseases (Box 6), including autoimmune hepatitis (Box 7).

A very large number of different drugs have been associated with liver injury. There is a clear difference in the documentation or the evidence for hepatotoxicity associated with these drugs. Isoniazid, phenytoin, disulfiram, amoxicillin/clavulanate, halothane and chlopromazine are drugs with well characterized hepatotoxicity. More recently antibiotics (amoxicillin/clavunalate, erytromicin, flucloxacillin, trimethoprim-sulpha, nitrofurantoin, isoniazid and rifampicin), analgesics and NSAIDs (diclofenac, dextropropoxyphene, paracetamol, ibuprofen) probably the most common type of drugs associated with DILI. In hospitalized patients, antineoplasic agents seem to commonly lead to DILI and are probably underreported. In a Spanish pharmacovigilance prospective program based on laboratory signals at hospital all patients with liver test abnormalities (x 3 upper limits of normal) were evaluated being antibiotics (19.5%), hormonal contraceptives (14.6%) and anticancer agents (10%) were the most frequent drug-groups associated to liver injury. In out-patients, the single most common drug implicated in ine series was diclofenac. Among patients with acute liver failure resulting from drugs in the US who underwent liver transplantation, paracetamol (acetaminophen) was the most common causative drug, followed by isoniazid, propylthiouracil, phenytoin and valproate.. Herbal and dietary supplements are implicated in approximately 11% of patients who developed acute serious liver disease of unknown cause in Spain.

The expectrum of DILI is varied, acute liver injury with or without jaundice, chronic hepatitis, although rare, liver cirrhosis has been reported to occur with long-standing drug treatment suspected to have caused DILI, and approximately 25-30% of DILI present with symptom of immunoallergic drug reactions. Table 2 showed the most common types of liver injury that have been identified with drugs.

9. Drugs for gastrointestinal diseases and their implication in adverse reactions

Most of adverse reactions with drugs used for treating gastrointestinal diseases are proton pump inhibitors. New antiTNF drugs, steroids and immunosuppressant in general used for

Type	Drugs
Acute liver injury	Isoniazid, disulfiram, paracetamol
Chronic hepatitis	Phenytoin, isoniazid
Autoimmune hepatitis	Minocycline, nitrofurantoin
Granulomatous hepatitis	Carbamazepine, quinidine
Steatohepatitis	Amiodarone, valproate
Cholestatic hepatitis	Flucloxacillin, amoxicillin/clavulanate
Bland cholestasis	Estrogens, nimesulide
Ductopenia	Amoxicillin, Trimethoprim-sulpha
Fibrosis	Methotrexate
Nodular regenerative hyperplasia	Azathioprine, 6-thioguanine

Table 2. Types of DILI (adapted from Björnsson)

inflammatory bowel disease cause also adverse drug reactions but the extended use of IBP makes them responsible of most of the adverse reactions with gastrointestinal drugs: hypergastrinemia, hypomagnesemia, tumors and, recently, enteric infections, pneumonia and osteoporosis (Maffei, 2007). There is a controversy about the probability of some of theses adverse drug reactions with IBPs. In the recent review by Thomson (2010) they failed to found risk of carcinoid tumors, cancer or nosocomial pneumoniae. There still controversy about the risk of osteoporosis with the long term use of IBPs.

10. Strategies to diminish adverse drugs reactions

The main strategies for reducing adverse drug reactions are: drug interaction calculators, renal insufficiency calculators, prescribing programs and collaboration between pharmacists, pharmacologists and clinical physicians.

The world Health Organization defines pharmacovigilance as the science and activities related to the detection, assessment, understanding, and prevention of adverse affects or any other possible drug-related problem. The field has grown significantly in recent years as postapproval safety studies for new medication become increasingly required, encompassing retrospective analysis of heath-care claims databases, meta-analysis, patients registries, and prospective case-control studies.

Recognition, reporting and careful characterization of these troubling, often unexpected ADRs are vital to future prevention of these event because detection of patterns and common features of ADRs can enhance our understanding of new mechanism and risk factors. The expansion of electronic database capabilities in hospital and primare-care setting offers the promise of better safety-based detection and monitoring systems that can detect ADRs earlier and prevent ADRs in the future. Hospital informatics systems linking to electronic medical records and including patient genotype with medication ordering and dispensing will reduce medication errors and inappropriate prescribing while improving

detection of ADRs. Also, the review of prescription by pharmacists can achieve a diminution in the appearance of adverse drug reactions.

It´s also important to recognize people specially susceptible to ADRs: elderly, women, polipharmacy, renal insufficiency and presence of drug-drug interactions. In this special population we have to be careful with prescription of new drugs and its dosing.

11. Conclusions

Adverse drug reactions is a very frequent problem that affects specially the gastrointestinal tract, being GI bleeding the most common adverse drug reaction causing hospital admission. Patients predisposed to suffer ADRs are elderly, women, renal insufficiency, polipharmacy and drug-drug interactions. Drugs used for treat gastrointestinal disease are quite sure but can b e implicated in ADRs as IBPs, imunosupre4ssants used for autoimmune hepatitis or inflammatory bowel disease. Recognition of this problem is increasing in frequency and new drugs can be responsible for new ADRs. Collaboration between clinician, pharmacists and pharmacology specialists is needed.

12. Appendix 1

ICH Guideline on E2D post-approval drug safety defined an adverse drug reaction (ADR) and a serious adverse drug reactions (SADR) as follows:

An adverse drug reaction, as established by regional regulations, guidance and practices, is concern noxious and unintended responses to a medicinal product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction".

Serious adverse event /ADR. In accordance with ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe),
- is a congenital anomaly/birth defect,
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in a emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

13. Appendix 2

Subject Information	
1. Temporal relationship of start of drug to ALT>2x ULN	Score
Initial treatment 5–90 days; subsequent treatment course: 1–15 days	2
Initial treatment <5 or >90 days; subsequent treatment course: >15 days	1
From cessation of drug: ≤15 days, or ≤15 days after subsequent treatment	1
Otherwise	0
2. After drug cessation- difference between peak ALT and upper limits normal	
Decreases >50% within 8 days	3
Decreases >50% within 30 days	2
No information or decrease >50% after >30 days, or inconclusive	0
Decrease <50% after 30 days or recurrent increase	-2
3. Risk factors	
No alcohol use	0
Alcohol use	1
Age ≤55 years	0
Age >55 years	1
4. Concomitant drug	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
5. Nondrug causes: Six are primary: recent hepatitis A, B, or C, biliary obstruction, acute alcoholic hepatitis (AST > 2x ALT), recent hypotension Secondary group: Underlying other disease; possible CMV, EBV or HSV infection	
All primary and secondary causes reasonably ruled out:	2
All 6 primary causes ruled out	1
4 or 5 primary causes ruled out	0
< 4 primary causes ruled out (max. negative score for items 4 and 5: –4)	-2
Nondrug cause highly probable	-3
6. Previous information on hepatotoxicity of the drug in question	
Package insert or labelling mention	2
Published case reports but not in label	1
Reaction unknown	0
7. Rechallenge	
Positive (ALT doubles with drug in question alone)	3
Compatible (ALT doubles with same drugs as given before initial reaction) +1	1
Negative (Increase in ALT but <2x ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0
Total (range of algebraic sum: –8 to +14)	
Score Interpretation: Highly probable >8; Probable 6–8; Possible 3–5; Unlikely 1–2; Excluded <0	

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Table 1. RUCAM Hepatocellular Injury Scale

Subject Information	
1. Temporal relationship of start of drug to ALP>2x ULN	Score
Initial treatment 5–90 days; subsequent treatment course: 1–90 days	2
Initial treatment <5 or >90 days; subsequent treatment course: >90 days	1
From cessation of drug: ≤30 days, or ≤30 days after subsequent treatment	1
Otherwise	0
2. After drug cessation - difference between peak ALP or total bilirubin and ULN	
Decreases ≥50% within 180 days	2
Decreases <50% within 180 days	1
Persistence or increase or no information	0
If drug is continued – inconclusive	0
3. Risk factors	
No alcohol use	0
Alcohol use	1
Age ≤55 years	0
Age >55 years	1
4. Concomitant drug	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
5. Nondrug causes: Six are primary: recent hepatitis A, B, or C, biliary obstruction, acute alcoholic hepatitis (AST > 2x ALT), recent hypotension Secondary group: Underlying other disease; possible CMV, EBV or HSV infection	
All primary and secondary causes reasonably ruled out:	2
All 6 primary causes ruled out	1
4 or 5 primary causes ruled out	0
< 4 primary causes ruled out (max. negative score for items 4 and 5: –4)	-2
Nondrug cause highly probable	-3
6. Previous information on hepatotoxicity of the drug in question	
Package insert or labelling mention	2
Published case reports but not in label	1
Reaction unknown	0
7. Rechallenge	
Positive (ALT doubles with drug in question alone)	3
Compatible (ALT doubles with same drugs as given before initial reaction) +1	1
Negative (Increase in ALT but <2x ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0
Total (range of algebraic sum: –8 to +14)	
Score Interpretation: Highly probable >8; Probable 6–8; Possible 3–5; Unlikely 1–2; Excluded <0	

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Table 2. RUCAM Cholestatic or Mixed Liver Injury Scale

Any one of the following:
• More than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT)
• More than or equal to twofold elevation above the ULN for alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of 5′-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone pathology
driving the rise in ALP level)
• More than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2× ULN
Level of evidence: 2b (exploratory/retrospective cohort studies)

Box 1. clinical chemistry criteria for drug-induced liver injury (DILI) (adapted from Aithal et al. 2011)

• Pattern of liver injury is based on earliest identified liver chemistry elevations that qualify as DILI (Box 1)
• Pattern of liver injury is defined using R value where R =(ALT/ULN)/(ALP/ULN). This will require estimation of alanine aminotransferase (ALT) (aspartate transaminase is used when ALT is unavailable) and alkaline phosphatase (ALP) from the same serum sample
• ALT activity = patient's ALT/upper limit of normal (ULN); ALP activity = patient's ALP/ULN; R = ALT activity/ALP activity
• Hepatocellular pattern of DILI = R ≥ 5
• Mixed pattern of DILI = R > 2 and < 5
• Cholestatic pattern of DILI = R ≤ 2
• Histological summary should be recorded separately (if liver biopsy has been performed). However, the liver biopsy interpretation will generally not replace the R value for purposes of classification
Level of evidence: 2b (retrospective cohort studies)

Box 2. criteria for classifying the clinical pattern of drug induced liver injury (DILI) (adapted from Aithal et al. 2011)

Category	Severity	Description
1	Mild	Elevated alanine aminotransferase/alkaline phosphatase (ALT/ALP) concentration reaching criteria for DILI* but bilirubin concentration <2× upper limit of normal (ULN)
2	Moderate	Elevated ALT/ALP concentration reaching criteria for DILI* and bilirubin concentration ≥2× ULN, or symptomatic hepatitis
3	Severe	Elevated ALT/ALP concentration reaching criteria for DILI*, bilirubin concentration ≥2× ULN, and one of the following: • International normalized ratio ≥1.5 • Ascites73 and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis31 • Other organ failure considered to be due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

Box 3. DILI severity index (adapted from Aithal et al. 2011)

• The Roussel Uclaf Causality Assessment Method (RUCAM) scale should be used for causality assessment (Appendix 2)
• If more than one drug is suspected to be causing DILI, the RUCAM scale should be applied to each drug separately. If such assessments are not practical (e.g., antituberculosis medications), all the drugs involved may be implicated as a single entity.
• If more than one drug is rated "possible" or higher by RUCAM, evaluation should be sought by a specialist to rank the drugs by order of likelihood of causing DILI. This may be done on the basis of the signature pattern of DILI and a review of the literature.
Level of evidence: 1b (validating cohort studies)

Box 4. DILI causality assessment (adapted from Aithal et al. 2011)

• Initial clinical episode met the criteria to qualify as acute DILI (Box 1)
• Initial episode on causality assessment has been considered possible, probable, or highly probable DILI on the basis of Roussel Uclaf Causality Assessment Method scoring criteria (Appendix 2).
Persistent DILI is defined as evidence of continued liver injury after withdrawal of the causative agent, beyond 3 months of follow-up for hepatocellular and mixed DILI, and beyond 6 months for cholestatic DILI
• Chronic DILI is defined as evidence of continued liver injury after withdrawal of the causative agent beyond 12 months of follow-up, regardless of the classification of DILI
• There is no new risk factor other than exposure to the suspect drug that would explain the persistence of liver injury, and other causes of chronic liver diseases have been excluded
Level of evidence: 4 (prognostic cohort studies of modest quality)

Box 5. Characteristics of persistent and chronic druginduced liver injury (DILI) (adapted from Aithal et al. 2011)

• Evidence of chronic liver disease is established on the basis of validated methods such as clinical evidence of cirrhosis, histological evidence of chronic liver disease, and imaging in cases of vascular disorder and tumours, as appropriate
• Evidence of drug intake for an appropriate duration preceding the appearance of symptoms, signs, or test results suggestive of chronic liver disease
• Exclusion of other etiologies of chronic disease (outlined in Supplementary Appendix 2, table S3)
Level of evidence: 1b (prospective/validating cohort studies with good follow-up)

Box 6. characteristics of drug-associated chronic liver disease (adapted from Aithal et al. 2011)

• The score is ≥6 points on simplified diagnostic criteria for AIH (scores >6 points with the simplified criteria can be obtained if liver biopsy is performed. Hennes *et al.*()consider a probable diagnostic score to be ≥6)
• Injury resolves on withdrawal of medication that triggered the AIH, with or without immunosuppressive therapy to induce remission
• No relapse within a period of 1 year after withdrawal of all immunosuppressants. This criterion needs further confirmation and cannot be considered pathognomonic because it is quite variable depending on the cohorts analyzed
Level of evidence: 2b (exploratory cohort study)

Box 7. Characteristics of drug-induced autoimmune hepatitis (AIH) (adapted from Aithal et al. 2011)

14. References

Aithal GP, Day CP. Hepatic adverse drug reactions. En: Pharmacovigilance. Chichester: John Wiley & Sons Ltd; p. 429-43 (2006.).

Aithal, G.P., Watkins P.B., Andrade, R.J., Larrey, D., Molokhia, M., Takikawa, H., Hunt, C.M., Wilke, R.A:, Avigan, M., Kaplowitz, N., Bjornsson, E. and Daly, A.K. Case definition and phenotype Standardization in Drug-induced Liver Injury. Clin Pharmacol Ther.89(6): 806-815.

Aronson, J.K. Adverse drug reactions—no farewell to harms. Br J Clin Pharmacol. ;63(2):131-135 (2007).

Balani AR, Grendell JH.Drug Saf. 2008;31(10):823-37.Drug-induced pancreatitis : incidence, management and prevention.

Bates, D.W., Spell, N., Cullen, D.J., Birdick, E., Laird, N., Petersen, L.A., Small, S.D., Boddie, J., Sweitzer, B.J., Leape, L.L. The cost of adverse drug events in hospitalized patients. JAMA. 277(4): 307-311 (2007).

Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol. 1993 Nov;46(11):1331-1336

Beppu K, Osada T, Shibuya T, Watanabe SPathogenic mechanism of NSAIDs-induced mucosal injury in lower gastrointestinal tract. Nihon Rinsho. 2011 Jun;69(6):1083-7

Björnsson, E., Jerlstad, P., Bergqvist, A. & Olsson, R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand. J. Gastroenterol. 40, 1095–1101 (2005).

Björnsson E. Review article: drug-induced liver injury in clinical practice. Aliment Pharmacol ther; 32: 3-12 (2010)

Budnitz, D.S., Pollock, D.A., Weidenbach, K.N., Mendelsohn, A.B., Schoeder, T.J., Annest, J.L. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 296 (15), 1858-1866 (2006).

Carrasco-Garrido P*, López de Andrés A, Hernández Barrera V, Gil de Miguel A, Jiménez García R. Trends of adverse drug reactions related hospitalizations in Spain (2001-2006). BMC Health Services Research 2010, 10:287.
http://www.biomedcentral.com/1472-6963/10/287

Cecile M, Seux V, Pauly V, Tassy S, Reynaud-Levy O, Dalco O, Thirion X, Soubeyrand J, Retornaz F. Adverse drug events in hospitalized elderly patients in a geriatric medicine unit: study of prevalence and risk factors. Rev Med Interne. 2009 May;30(5):393-400.

Cheng, C.M. Hospital systems for detection and prevention of adverse drug events. Clin Pharmacol Ther. 89: 779-781 (2011)

Clark K, Byfieldt N, Dawe M, Currow DC. Treating Constipation in Palliative Care: The Impact of Other Factors Aside From Opioids. Am J Hosp Palliat Care. 2011 May 23.

Classen, D.C., Pestotnik, S.L., Evans, R.S., Loyds, J.F., Burke, J.P. Adverse drug events in hospitalized patients. Excess length of stay, extra cost, and attributable mortality. JAMA. 277 (4),301-6 (1997).

Classen, D.C., Pestonik, S.L., Evans, R.S., Burke, J.P. Computerized surveillance of adverse drug event in hospital patients. Qua.l Saf. Health Care. 14, 221–226 (2005).

Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993 Nov;46(11):1323-1330.

de Abajo, F.j., Montero, D., Madurga, M. & García Rodríguez, L.A. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br. J. Clin. Pharmacol. 58, 71–80 (2004).

De Valle MB, Av Klinteberg V, Alem N, Olsson R, Björnsson E. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. Aliment Pharmacol Ther 2006; 24: 1187-95

Devi DP, Sushma M, Guido S. Drug-induced upper gastrointestinal disorders requiring hospitalization: a five-year study in a South Indian hospital. Pharmacoepidemiol Drug Saf. 2004 Dec;13(12):859-62

Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. Crit Care Med. 2010 Jun;38(6 Suppl):S231-43.

Fontana RJ, Watkins PB, Bonkowsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group Drug-induced Liver Injury Network (DILIN) prospective study: rationale, design and condunt. Drug Saf; 32: 55-68 (2009)

Frazier, T.H. & Krueger, K.j. Hepatotoxic herbs: will injury mechanisms guide treatment strategies? Curr. Gastroenterol. Rep. 11, 317–324 (2009).

Gautier, S., Bachelet, H., Bordet, R., Caron, J. The cost of adverse drug reactions. Expert Opinion on Pharmacotherapy. 4(3): 319-326 (2003)

Gurwitz, J.H., Field, T.S., Harold, L.R., Rothschild, J., Debellis, K., Seger, A.C., Cadoret, C., Fish, L.S., Garber, L., Kelleher, M., Bates, D.W. Incidence and preventability of adverse drug events among elder persons in the ambulatory setting. JAMA. 289 (9), 1107—1116 (2003).

Grenouillet-Delacre, M., Verdoux, H., Moore, N., Haramburu, F., Miremont-Salamé, G., Etienne, G., Robinson, P., Gruson, D., Hilbert, G., Gabinski, C., Bégaud, B., Molimard, M. Life-threatening adverse drug reactions at admission to medical intensive care: a prospective study in a teaching hospital. Intensive Care Med. Dec;33(12):2150-7 (2007).

Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients.Arch Intern Med. 2011 Jun 13;171(11):1013-9.

Ibanez L, Perez E, Vidal X, Laporte JR. Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol ; 37: 592–600 (2002)

ICH Guideline on E2D Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting. London, 20 November 2003 CPMP/ICH/3945/03.

ICH Guideline on E2A Clinical Safety data Management: definitions and Standards for expedited Reporting E2A. Current Step 4 version, dated 27 October 1994 (CPMP/ICH/377/95)

Johnson, J.A., Bootman, J.L. Drug-related morbidity and mortality; a cost of illness model. Arch. Intern. Med. 155, 1949-56 (1995).

Kane-Gill, S.L., Van Den Bos, J. & Handler, S.M. Adverse drug reactions in hospital and ambulatory are setting identified using a large administrative database. Ann. Pharmacother. 44, 983-993 (2010).

Karch, F.E., Lasagna, L. Toward the operational identification of adverse drug reactions. Clin. Pharmacol. Ther. Mar;21(3):247-254 (1977).

Kaur S, Vinod Kapoor,[1] Rajiv Mahajan,[1] Mohan Lal,[2] and Seema Gupta. Monitoring of incidence, severity, and causality of adverse drug reactions in hospitalized patients with cardiovascular disease. Indian J Pharmacol. 2011 February; 43(1): 22–26.

Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic rview of prospectgive observational studies. Ann Pharmacother. 2008 Jul;42(7):1017-25.1

Kunac DL, Kennedy J, Austin N, Reith D. Incidence, preventability, and impact of Adverse Drug Events (ADEs) and potential ADEs in hospitalized children in New Zealand: a prospective observational cohort study. Paediatr Drugs. 2009;11(2):153-60.

Kurahara K, Matsumoto T, Iida M.. Characteristics of nonsteroidal anti-inflammatory drugs-induced colopathy Nihon Rinsho. 2011 Jun;69(6):1098-103.

Kutty P, Woods CW, Arlene C. Sena, Stephen R. Benoit, Susanna Naggie,,Joyce Frederick, Sharon Evans, Jeffery Engel, and L. Clifford McDonald. Risk Factors for and Estimated Incidence of Community-associated Clostridium diffi cile Infection, North Carolina, USA1Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 2, February 2010

Lancashire RJ, Cheng K, Langman MJ. Discrepancies between population-based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. Aliment Pharmacol Ther 2003 Apr 1;17(7):887–93.

Lammert C, Einarsson S, Saha C, Niklasson A, Bjornsson E, Chalasani N. Relationship between daily dose of oral medications and idiosyncrativ drug-induced liver injury: sear for signals. Hepatology 2008; 47: 2003-9

Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis; 22: 145–55 (2002).

Lat I, Foster DR, Erstad B. Drug-induced acute liver failure and gastrointestinal complications.Crit Care Med. 2010 Jun;38(6 Suppl):S175-87

Lazarou, J., Pomeranz, B.H., Corey, P.N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279 (15), 1200-5 (1998).

Leape, L.L., Brennan, T.A., Laird, N., Lawthers, A.G., Localio, A.R., Barnes, B.A., Hebert, L., Newhouse, J.P., Weiler, P.C., Hiatt, H. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. NEJM. 324 (6), 377-84 (1991).

Leung FW, Rao SS. Approach to fecal incontinence and constipation in older hospitalized patients. Hosp Pract (Minneap). 2011 Feb;39(1):97-104.

Leventhal, J.M., Hutchinson, T.A., Kramer, M.S., Feinstein, A.R. An algorithm for the operational assessment of adverse drug reactions. III. Results of tests among clinicians. JAMA. Nov 2;242(18):1991-1994 (1979).

Maffei M, Desmeules J, Cereda JM, Hadengue A. Side effects of proton pump inhbitors (PPIs). Rev Med Suiss 2007; 5(3): 1934-36, 1938.

Mallet, L, Spinewine, A, Huang, A. The challenge of managing drug interactions in elderly people. Lancet. 370(9582):185-191 (2007).

Mannesse, C.K., Derkx, F.H., de Ridder, M.A., Man in 't Veld, A.J., van der Cammen, T.J. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing. 29(1):35-39 (2000).

Meier Y, Cavallaro M, Roos M, et al. Incidence of drug-induced liver injury in medical inpatients. Eur J Clin Pharmacol; 61: 135–43 (2005).

Mino-León D, Galván-Plata ME, Doubova SV, Flores-Hernandez S, Reyes-Morales H. A pharmacoepidemiological study of potential drug interactions and their determinant factors in hospitalized patients. Rev Invest Clin. 2011 Mar-Apr;63(2):170-8.

Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A., et al. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. Ago;30(2):239-245 (1981).

Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. Best Practice & Research Clinical Gastroenterology 24 (2010) 143–155

O'Grady, j.G. Acute liver failure. Postgrad. Med. J. 81, 148–154 (2005).

Onder, G., Petrovic, M., Tangíísuram, B., Meinardi, M.C., Markito-Notenboom W.P., Somers, S., Rajkumar, C., Bernabei, R., van der Cammen T.J.M. Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 years or older. Arch. Intern. Med. 170(13): 1142-1148 (2010).

Ostapowicz, G. et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann. Intern. Med. 137, 947–954 (2002).

Ouwerkerk J, Boers-Doets COuwerkerk J, Boers-Doets C. Best practices in the management of toxicities related to anti-EGFR agents for metastatic colorectal cancer. Eur J Oncol Nurs. 2010 Sep;14(4):337-49

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK & Breckenridge AM. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 329,15-9 (2004).

Ramachandran, R. & Kakar, S. Histological patterns in drug-induced liver disease. J. Clin. Pathol. 62, 481–492 (2009).

Ramirez E, Carcas AJ, Borobia AM, Lei SH, Piñana, E, Fudio S & Frias J A Pharmacovigilance Program From Laboratory Signals for the Detection and Reporting of Serious Adverse Drug Reactions in Hospitalizad Patients. Clin Pharmacol Ther. 87 (1): 74-86.

Russo MW, Galanko jA, Shrestha R, Fried MW & Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 10, 1018–1023 (2004).

Sánchez Muñoz-Torrero JF, Barquilla P, Velasco R, Fernández Capitán MC, Pacheco N, Vicente L, & all. Adverse drug reactions in internal medicine units and associated risk factors. Eur J Clin Pharmacol (2010) 66:1257–1264

Sgro, C. et al. Incidence of drug-induced hepatic injuries: a French populationbased study. Hepatology 36, 451–455 (2002).

Tai-Yin Wu, Min-Hua Jen, Alex Bottle, Mariam Molokhia, Paul Aylin, Derek Bell, Azeem Majeed. Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009 J R Soc Med 2010: 103: 239–250. DOI 10.1258/jrsm.2010.100113

Watkins, P.B., Seligman, P.j., Pears, j.S., Avigan, M.I. & Senior, j.R. Using controlled clinical trials to learn more about acute drug-induced liver injury. Hepatology 48, 1680–1689 (2008).

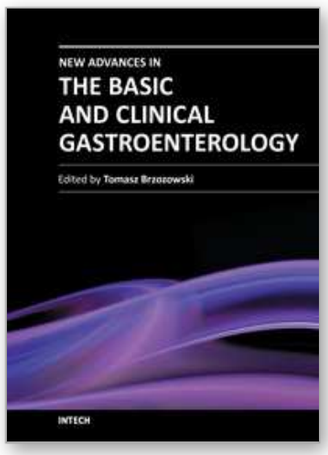
Wawruch M, Macugova A, Kostkova L, Luha J, Dukat A, Murin J, Drobna V, Wilton L, Kuzelova M The use of medications with anticholinergic properties and risk factors for their use in hospitalised elderly patients. Pharmacoepidemiol Drug Saf. 2011 Jun 13. doi: 10.1002/pds.2169.

Wester K, Jönsson A, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacology 2008 / 65:4 / 573–579

White, R.A., Xu, H., Denny, J.C., Roden , D.M., Krauss, R.M., McCarty, C.A., Davis, R.L., Skaar, T., Lamba, J., Savoga, G. The emerging role of electronic medical records in pharmacogenomics. Clin. Pharmmacol. Ther. 89, 379-386 (2011)

Wikman-Jorgensen, López-Calleja E, Safont-Gasó P, Matarranz-del-Amo M, Andrés Navarro R & Merino-Sánchez J. Antiagregation and anticoagulation, relationship with upper gastrointestinal bleeding. Rev Esp Enferm Dig 2011; 103: 360-365.

Zopf Y, Rabe C, Neubert A, Hahn EG, Dormann H. Risk factors associated with adverse drug reactions following hospital admission: a prospective analysis of 907 patients in two German university hospitals. Drug Saf. 2008;31(9):789-98.



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The purpose of this book was to present the integrative, basic and clinical approaches based on recent developments in the field of gastroenterology. The most important advances in the pathophysiology and treatment of gastrointestinal disorders are discussed including; gastroesophageal reflux disease (GERD), peptic ulcer disease, irritable bowel disease (IBD), NSAIDs-induced gastroenteropathy and pancreatitis. Special focus was addressed to microbial aspects in the gut including recent achievements in the understanding of function of probiotic bacteria, their interaction with gastrointestinal epithelium and usefulness in the treatment of human disorders. We hope that this book will provide relevant new information useful to clinicians and basic scientists as well as to medical students, all looking for new advancements in the field of gastroenterology.

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