Risk of drug induced pancreas injury (DIPI) with anti-psychotics – experience with Seroquel(quetiapine fumarate)

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Patrick Hu, M.D.
Senior Safety Physician

AstraZeneca

Outline

1. Background Information
2. Clinical Trial data
3. Post marketing data
4. Action taken : CDS updated information



Mechanism of action

- Quetiapine –
  - Serotonin and Dopamine antagonist (D1 and D2)
  - Alpha 1 and Alpha 2 adrenergic antagonist

- Norquetiapine is the major active metabolite which has anti-muscarinic activity

- No mechanism for pancreatitis in man or animals

- No pancreatic toxicity seen in toxicology studies

First Pancreatitis Published Report with Atypical Antipsychotics After Marketing in USA

Risperidone –marketed in 1994 and reported in1997

Clozapine – marketed in 1989 and reported in 1992

Olanzapine – marketed in 1986 and reported in 2004

Quetiapine – marketed in 1997 and reported in 2004

Ziprasidone – marketed in 2001 with no reported case

Aripiprazole- marketed in 2002 and reported in 2008

Labeledness of Pancreatitis

- All atypical antipsychotics have pancreatitis in their US Prescribing Information except for Ziprasidone.
- Aripiprazole , Clozapine and Seroquel(regular tablets) - pancreatitis during clinical trials
- Olanzapine –only seen post-marketing
- Risperidone – only seen post-marketing
- Clozapine is only atypical with pancreatitis in Warnings

AERS Database

Computerized Adverse Event Reporting System

Coded with the standardized terminology of the Medical Dictionary for Regulatory Activities (MedDRA).

Safety issues leading to drug withdrawal from the market have been discovered using the AERS database

Limitations of AERS

- No denominator
  - Population rates cannot be estimated.
- Differential under-reporting of events can bias results.
- MedDRA is often too granular
  - Numerous terms for seizures, strokes, etc.

Food Drug Administration (FDA) AERs data

An EB05 is the lower bounds of the two-sided 90% confidence interval around an EBGM, EBGM is the Empirical Bayes Geometric Mean - an adjusted estimate of the mean proportional reporting ratio that addresses small cell counts

Table 1 **FDA AERS database through 3Q2010: quetiapine and Pancreatitis (suspect and concomitant)**

Event	EB05 (N)
Pancreatitis (custom term)	9.213 (3241)

AERS Adverse Event Reporting System. EB05 lower boundary of the 90% confidence interval for the Empiric Bayesian Geometric Mean. MedDRA Medical Dictionary for Regulatory Activities.

Source of data

- ‘Sapphire’ is AstraZeneca’s global patient safety database that contains all AE reports, from spontaneous sources (eg, health care professionals, regulatory authorities, literature, consumers and others)and reports from clinical study use that is defined as serious.

- Non-serious reports from clinical study use are usually only entered into the clinical study database.



Clinical Trial Data

All placebo-controlled trials

- There were no adverse event reports of pancreatitis amongst quetiapine-treated patients

Table AE- 1 Number of patients with adverse events related to Pancreatitis (All Placebo-controlled trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk QTP vs PLA[d]	95% CI Lower	95% CI Upper
Pancreatic	Any	QTP	0 (0)	9327	1044.4	0.00	0.00	NA	NA
		Pla	3 (2)	4845	560.7	0.48			
	Pancreatitis	QTP	0 (0)	9327	1044.4	0.00			
		Pla	3 (2)	4845	560.7	0.48			
	Pancreatitis acute	QTP	0 (0)	9327	1044.4	0.00			
		Pla	0 (0)	4845	560.8	0.00			



Long-term relapse prevention trials

- There were no adverse event reports of pancreatitis amongst quetiapine-treated patients

Table AE-1 Number of patients with adverse events related to Pancreatitis (All long-term relapse prevention trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk QTP vs PLA[d]	95% CI Lower	95% CI Upper
Pancreatic	Any	QTP	0 (0)	2043	1026.0	0.00	0.00	NA	NA
		Pla	1 (1)	2016	704.3	0.15			
	Pancreatitis	QTP	0 (0)	2043	1026.0	0.00			
		Pla	1 (1)	2016	704.3	0.15			
	Pancreatitis acute	QTP	0 (0)	2043	1026.0	0.00			
		Pla	0 (0)	2016	704.3	0.00			

All trial data

- There were 9 adverse event reports of pancreatitis amongst quetiapine-treated patients (exposure adjusted incidence rate of 0.03 per 100 patient years

Table AE-1 Number of patients with adverse events related to Pancreatitis (All trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
Pancreatic	Any	QTP	9 (7)	27814	0.03	8509.6	0.11
	Pancreatitis	QTP	6 (4)	27814	0.02	8510.7	0.07
	Pancreatitis acute	QTP	3 (3)	27814	0.01	8510.1	0.04



All trial data

- All of the 9 reports for patients treated with quetiapine were confounded by either medical history and/or concomitant medications.
- Eight of the 9 adverse events were considered by the investigator to be not related to trial treatment.
- One non serious report was considered related to trial treatment.

Clinical trials: The only non-serious case

- 53-year-old female had a non-serious event of pancreatitis after 2 days on quetiapine, and recovered the next day. The patient was being treated with conjugated estrogens. The patient continued on SEROQUEL for **15 more days** and thereafter was discontinued due to lack of efficacy. No amylase or lipase laboratory values were provided. The patient had relevant medical history of cholecystectomy and hysterectomy (relative timing is unknown). The event was considered related by the investigator.



Post Marketing Data

Post Marketing Reports

- 3106 case reports : 2900 are legal reports.
- From the 206 (non-legal) cases, (164) medically confirmed, (42) non-medically confirmed

Legal Reports

- Of the 2900 legal reports reviewed, 1173 provided concurrent medical history/risk factors or current illness.
- 1274 reports provided information regarding concomitant medications for which pancreatitis has been reported.
- The remaining reports provided limited or no information regarding the cases.

Legal Reports

Legal reports are these reports that contend that plaintiffs have developed medical conditions and/or other injuries in association with medication use.

Limitations

- Frequently contain limited and/or lack of information regarding a temporal relationship to medication use, medical history, concomitant illness or medications.
- Lack of confirmation that a particular event occurred.

Post Marketing Reports

- Of the 164 case reports medically confirmed:

➢8 from clinical trial reports
➢5 described pancreatitis necrotizing or hemorrhagic
➢18 confounded by risk factors/medical history/alternative causes
➢30 confounded by medications for which pancreatitis has been reported
➢44 confounded by both risk factors/medical history and concomitant medications
➢59 contain insufficient information to draw a medical judgment.

CIOMS criteria for diagnosis of pancreatitis

- Characterized by recurrent or persisting abdominal pain.
- The presence of 2 of the following 3 manifestations:

- Persistent impairment of pancreatic exocrine function (clinically suspected by weight loss and signs of malabsorption) as demonstrated by appropriate tests
- Confirmation of morphological change in the pancreas as demonstrated by imaging techniques
- Abdominal or referred pain with or without pancreatic-enzyme changes

CIOMS

CIOMS : The Council for International Organizations of Medical Sciences

- An international, non-governmental, non-profit organization established jointly by WHO and UNESCO (the United Nations Educational, Scientific and Cultural Organization)
- CIOMS is representative of a substantial proportion of the biomedical scientific community
- **CIOMS Plays an important role within contemporary pharmacovigilance practice**



Post Marketing Reports

- There are 6 reports met CIOMS criteria for diagnosis of pancreatitis.

Individual Case Reports

Case 1: 37 year old female who had a medical history of increased triglycerides on SEROQUEL for 6 weeks reported to have a three-day epigastric pain and frequent vomiting. Hospitalized with Amylase of 1223 IU/L. Abdomen CT scan showed acute pancreatitis. No evidence of gallstones.

Individual Case Reports

Case 2: 30 year old female with no history of hypertriglyceridemia or alcohol use on SEROQUEL 200 mg/d (7 months) was hospitalized. Labs showed elevated triglycerides of 537. The patient was admitted for diabetic keotacidosis with elevated Amylase=550 IU/L and lipase=982 IU/L. Abdomen CT scan showed moderate acute pancreatitis. Abdominal ultrasound showed gallbladder sludge. SEROQUEL was discontinued. Patient recovered.

Individual Case Reports

Case 3: 8 year old male on SEROQUEL 25 mg/BID with medical history of bilateral hydronephrosis was hospitalized for pancreatitis four weeks after the start of SEROQUEL. Several weeks later, he developed abdominal pain and steatorrhea with normal pancreatic enzymes. He was diagnosed with pancreatic insufficiency. SEROQUEL was discontinued and replaced by ziprasidone. He had received valproate for unknown duration. He recovered with sequelae.

Individual Case Reports

Case 4: 30 year old male patient, medical history was not provided and he was concomitantly on haloperidol and valproate. The patient was hospitalized for pancreatitis. Seroquel was stopped. The patient recovered. On an unknown date, Seroquel XR was started and pancreatitis recurred and the patient was hospitalized. Outcome of the events was not provided. Additional information regarding the details of the report was requested and but not received. This report described a **possible positive dechallenge and rechallenge.**

Individual Case Report

Case 5: 43 year old male with history of alcoholism and increased triglycerides. Patient developed pancreatitis with increased triglycerides of 1890 (**baseline 295; units not provided**) after an unknown period of SEROQUEL treatment. Patient hospitalized and subsequently died.

Individual Case Reports

Case 6: 34 year old female was on SEROQUEL & valproate for approximately 2 months. Hospitalized with acute abdominal pain, vomiting, ketoacidosis, ketonuria and highly elevated triglycerides (83.6 mmol/L). All the symptoms are improved except abdominal pain. Abdominal CT showed acute pancreatitis. Patient was treated and recovered.

Time and dose relationship

- Time to onset ranging from **0** to **366** days.

- Doses ranging from **50** mg to **1900** mg per day at the time of the pancreatitis event.

Reports of positive dechallenge or positive rechallenge

- There were 8 reports identified as being a potential positive dechallenge or possible positive or negative rechallenge.
- All 8 reports have concurrent medications and/or diseases and/limited information.
- Limitation of possible potential positive dechallenge or possible positive rechallenge.

Difficulties in Assessment of Positive Dechallenge Cases and Positive Rechallenge Cases for pancreatitis

- Pancreatitis can be fatal and be self-limiting
- Some drugs can cause pancreatitis long after they are discontinued
- Pancreatitis may have recurring episodes with no drug exposure or effect.

Action taken: Updated CDS: Section 4.4

Pancreatitis

Pancreatitis **has been reported** in clinical trials and during the post marketing experience, however a causal relationship has not been established. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see Section 4.4 Lipids), gallstones, and alcohol consumption.

Summary

1. Background Information
2. Clinical Trial data
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THANK YOU

QUESTIONS AND DISCUSSION

Risk of drug induced pancreas injury (DIPI) with anti-psychotics – experience with Seroquel (quetiapine fumarate)

BACK-UP SLIDES

Risk of drug induced pancreas injury (DIPI) with anti-psychotics – experience with Seroquel/Seroquel XR (quetiapine fumarate)

Back up slide 1

- Potential mechanisms
- The proposed mechanism of action for clozapine-induced pancreatitis includes the possibility that clozapine has exocrine and possibly toxic effects on the salivary and pancreatic tissues. Pancreatitis has not been causally related to SEROQUEL/SEROQUEL XR.

Classification system of drug-induced acute pancreatitis

Class Ia drugs
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ib drugs
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II drugs
At least 4 cases in the literature
Consistent latency (≥75 percent of cases)
Class III drugs
At least 2 cases in the literature
No consistent latency among cases
No rechallenge
Class IV drugs
Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge

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Etiology of acute pancreatitis

Mechanical	Gallstones, biliary sludge, ascariasis, periampullary diverticulum, pancreatic or periampullary cancer, ampullary stenosis, duodenal stricture or obstruction
Toxic	Ethanol, methanol, scorpion venom, organophosphate poisoning
Metabolic	Hyperlipidemia (types I, IV, V), hypercalcemia
Drugs	Didanosine, pentamidine, metronidazole, stibogluconate, tetracycline furosemide, thiazides, sulphasalazine, 5-ASA, L-asparaginase, azathioprine, valproic acid, sulindac, salicylates, calcium, estrogen
Infection	Viruses-mumps, coxsackie, hepatitis B, CMV, varicella-zoster, HSV, HIV
	Bacteria-mycoplasma, Legionella, Leptospira, salmonella
	Fungi-aspergillus
	Parasites-toxoplasma, cryptosporidium, Ascaris
Trauma	Blunt or penetrating abdominal injury, iatrogenic injury during surgery or ERCP (sphincterotomy)
Congenital	Cholodochocele type V, ? pancreas divisum
Vascular	Ischemia, atheroembolism, vasculitis (polyarteritis nodosa, SLE)
Miscellaneous	Post ERCP, pregnancy, renal transplantation, alpha-1-antitrypsin deficiency
Genetic	CFTR and other genetic mutations

5-ASA: 5-aminosalicylic acid; CMV: cytomegalovirus; HSV: herpes simplex virus; HIV: human immunodeficiency virus; ERCP: endoscopic retrograde cholangiopancreatography; SLE: systemic lupus erythematosus; CFTR: cystic fibrosis transmembrane conductance regulator.

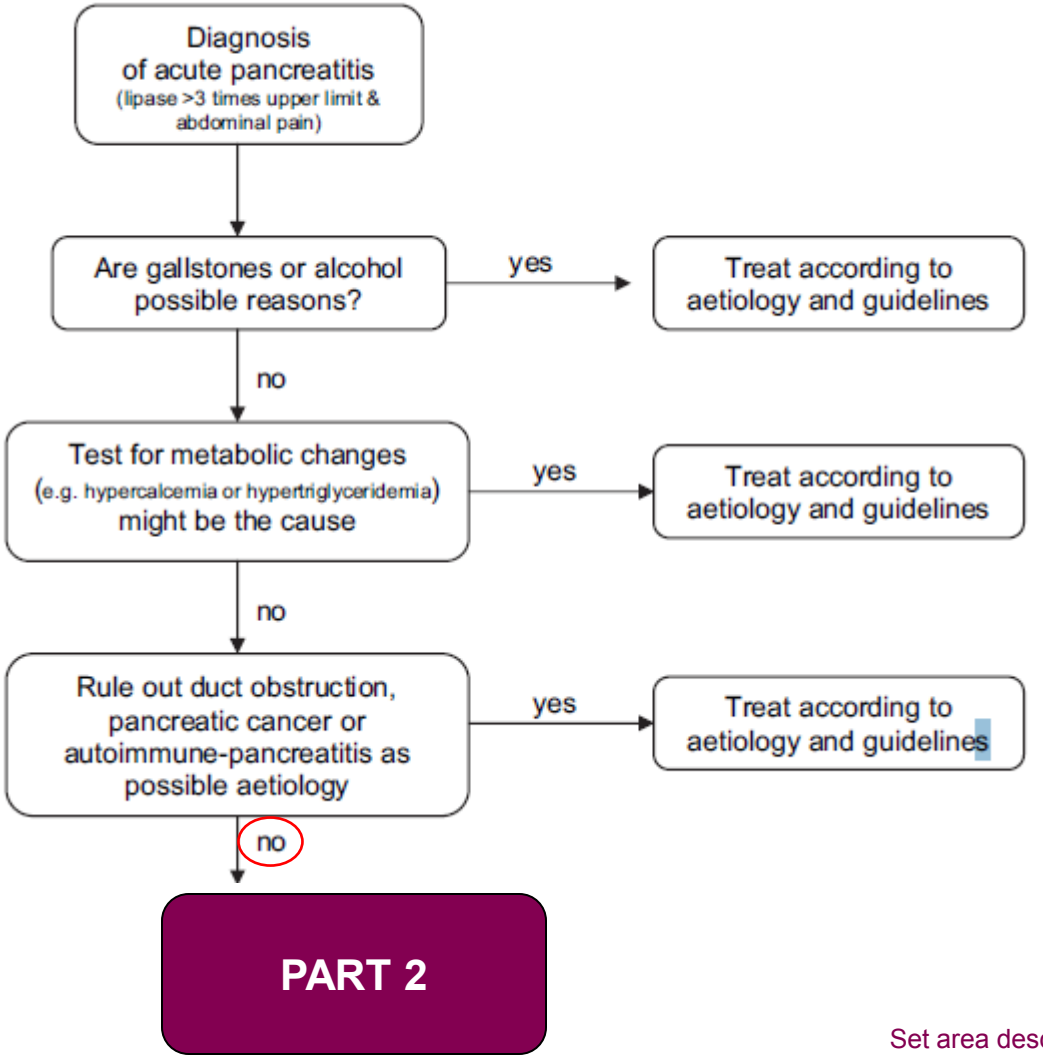
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Literature

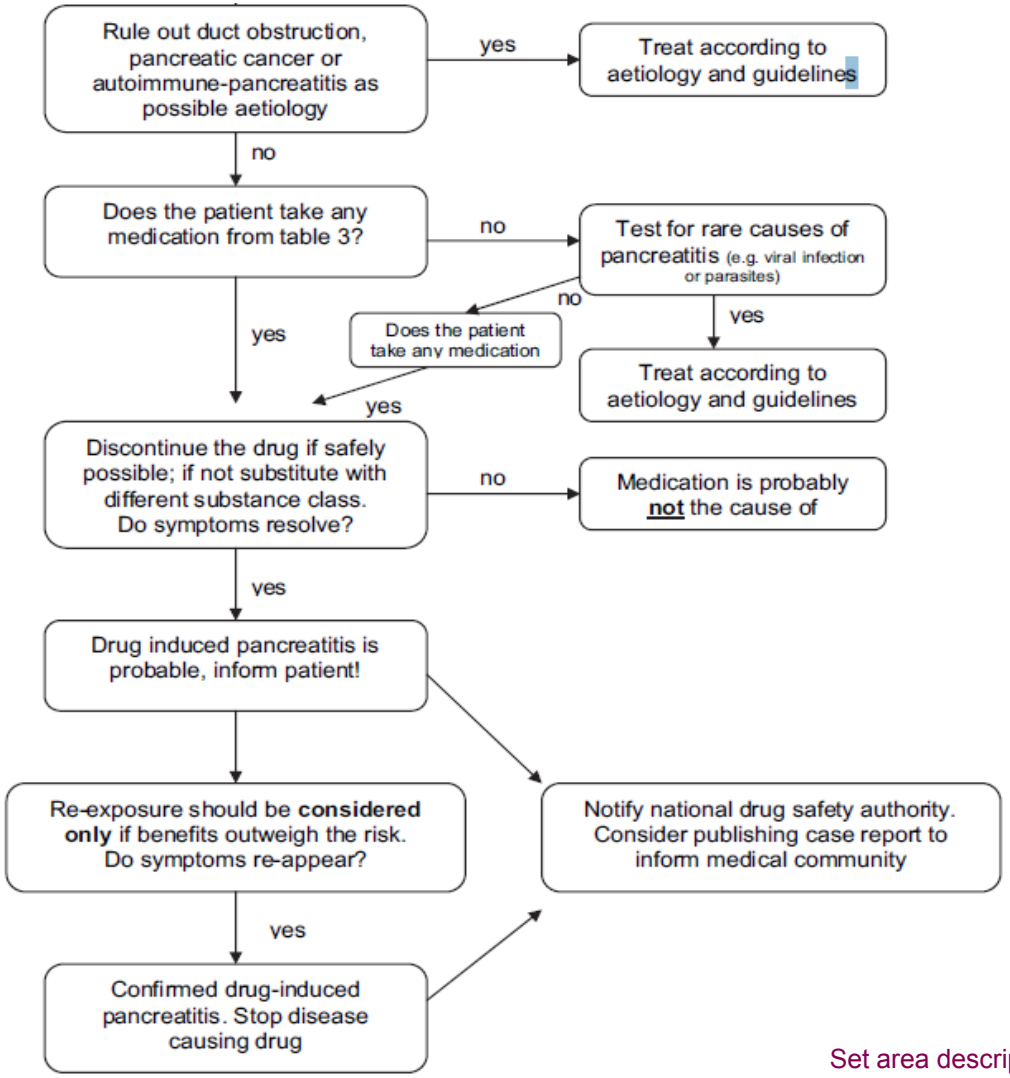
- A Population-based, case-control study to examine the association of atypical and conventional antipsychotics with the risk of hospitalization for acute pancreatitis.
- A trend was noted for increasing risk of hospitalization due to acute pancreatitis with decreasing potency of conventional antipsychotics.
- The conclusion was that current use of low-potency conventional, but not atypical, antipsychotics was associated with an increased risk of hospitalization for acute pancreatitis. (Gasse et al 2008)



Algorithm for the diagnosis of drug-induced pancreatitis (PART 1)



Algorithm for the diagnosis of drug-induced pancreatitis (PART 2)



Classification of evidence of drug induced pancreatitis

C.J. Nitsche et al. / Best Practice & Research Clinical Gastroenterology 24 (2010) 143–155

- **Definite Drug reaction** that follows a reasonable temporal sequence from administration of the drug that follows a known response pattern; that is confirmed by cessation of the drug (dechallenge); that is confirmed by reappearance of the symptoms upon repeated exposure to the drug (re-challenge)

- **Probable Drug reaction** that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern; that is confirmed by dechallenge; that could not be explained by the known characteristics of the patients clinical state

- **Possible Drug reaction** that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern;
- but that could have been produced by the patients clinical state or other modes of therapy administered to the patient



Classification of evidence of drug induced pancreatitis

NISON BADALOV,* et al. / CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:648–661

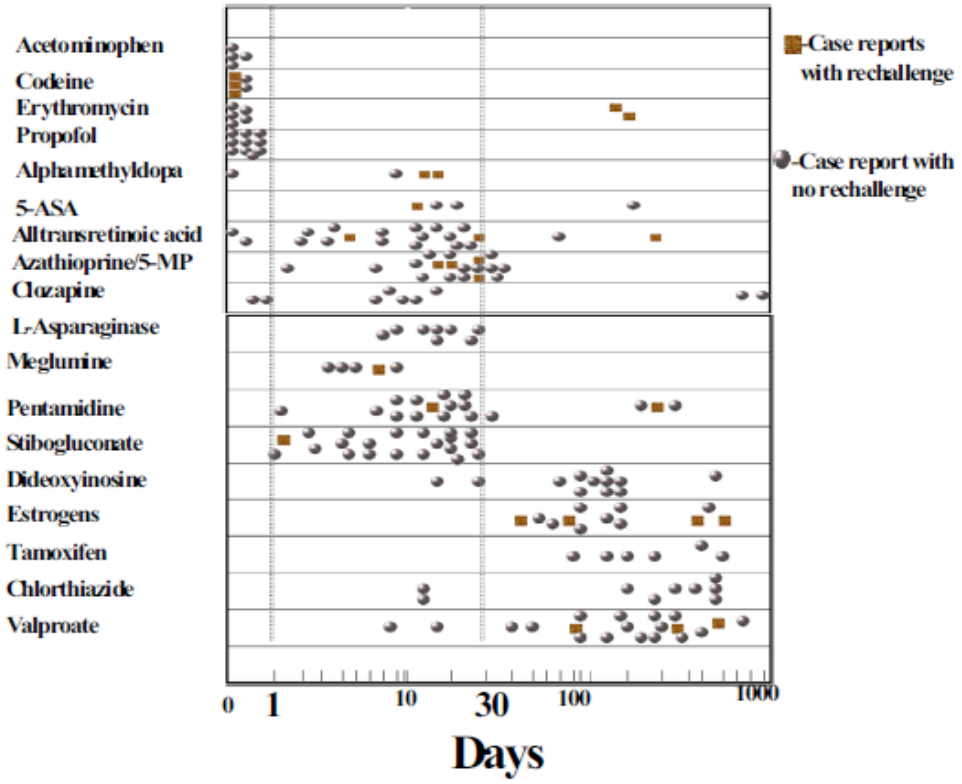


Figure 1. Drugs with a consistent latency (time between drug and onset of acute pancreatitis) in more than 75% of the cases (≥4 case reports). Three patterns of consistent latency were noted: short latency of less than 24 hours, an intermediate latency of greater than 24 hours and less than 30 days, and a long latency of greater than 30 days. ■, case reports with rechallenge; ◒, case reports with no rechallenge.

ANTIPSYCHOTICS

- Pre-90's
  - "Typical", conventional, traditional neuroleptics, major tranquilizors
  - Modeled on D_2 antagonism
  - EPS/TD
- Post-90's
  - "Atypical", novel, 2^{nd} generation
  - Modeled on 5-HT2/D2 antagonism
  - Less EPS, prolactin effects
  - Weight gain, sedation, diabetes



Classification of antipsychotic drugs

- **Typical antipsychotics**
  - Phenothiazines
    - e.g. chlorpromazine, fluphenazine, thioridazine
  - Butyrophenones
    - e.g. haloperidol, droperidol
  - Thioxanthines
    - e.g. chlorprotixen, thiothixene
- **Atypical antipsychotics**
  - Benzamides
    - remoxipride (investigational)
  - Diphenylbutylpiperazines
    - e.g. pimozide
  - Dibenzodiazepines

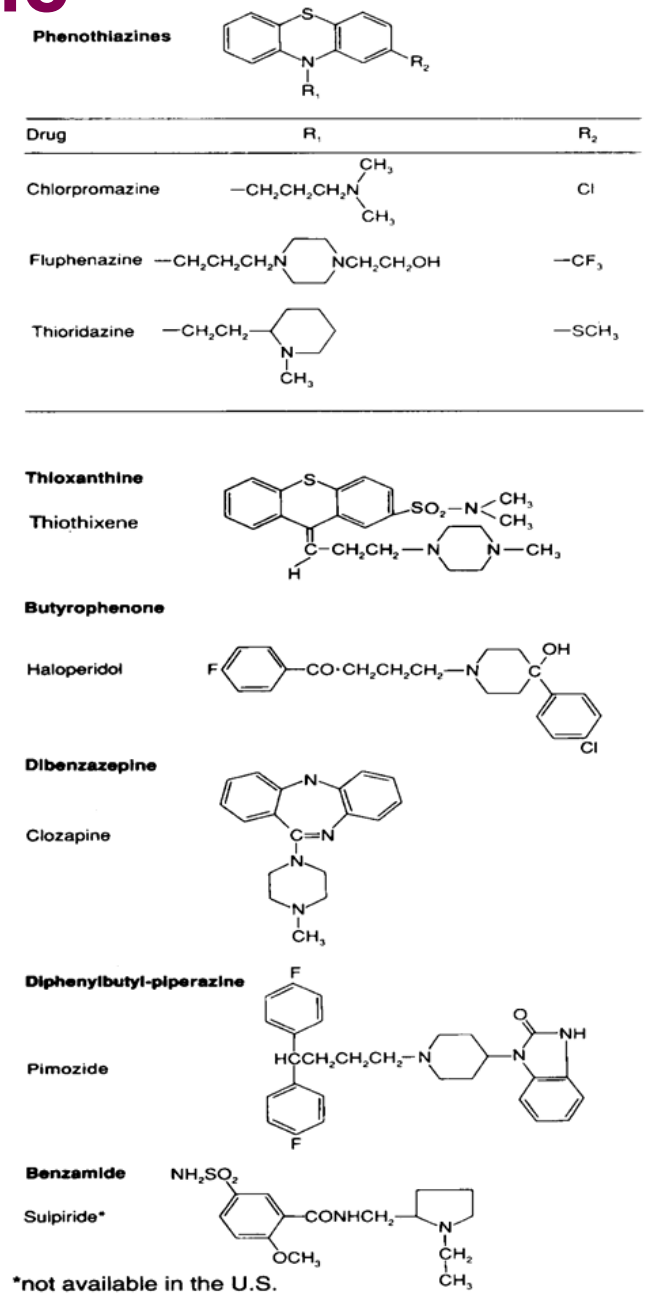


Fig. 28.2 Structures of neuroleptic drugs.

Clinical trials: patient narratives

- 5077IL/0014/0026/2602: (Case ID: 1994AP01706).
  43-year-old male patient with schizophrenia who had a history of alcohol abuse and drug dependence. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The event was considered not related by the investigator.

Clinical trials: patient narratives

- 5077IL/0050/0050/0008: (case ID: 1998PK45437) 54-year-old female with psychosis who had a medical history of abdominal surgery (Billroth II), chronic pancreatitis and endoscopic retrograde cholangiopancreatography (ERCP) with a subsequent perforation of the jejunum. The patient was on concomitant medication paracetamol for which pancreatitis has been reported. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The event was considered not related by the investigator.

Clinical trials: patient narratives

- D1447C00127/E0052018: (case ID: 2004UW23713) 50-year-old male with Bipolar I disorder who had a history of heavy alcohol use and was also taking valproate, for which pancreatitis has been reported. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The event was considered not related by the investigator.



Clinical trials: patient narratives

- D1441C00089/0082/23093: (Case ID: 2005UW00189) 58-year-old male with schizophrenia, paranoid type who had a history of alcohol dependency, borderline diabetes mellitus, and chronic pancreatitis and was also taking morphine, for which pancreatiis has been reported. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The event was considered not related by the investigator.



Clinical trials: patient narratives

- 5077IL/0056/0021/0015: (case ID: 1998UW46773) 24-year-old woman with schizoaffective disorder who had a medical history included gastritis, extrapyramidal syndrome, asthma, and obesity and was also taking clonazepam, valproic acid, and sertraline for which pancreatitis has been reported. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The investigator considered the pancreatitis to be not related to trial treatment.



Clinical trials: patient narratives

- 5077IL/0048/0003/0310: (case ID: 1996AP20116) 77-year old man whose (Serious) adverse event led to the patient's withdrawal from trial treatment. The patient had Alzheimer's disease and psychosis and a medical history of first-degree cardiac block; surgery for carcinoma of the colon; hernia repair; arthritis; and borderline, diet-controlled diabetes mellitus. Ferrous sulfate was the only ongoing concomitant medication The patient had multiple simultaneous (Serious) adverse events, including myocardial infarction. The patient died five days after the onset of the (Serious) adverse events. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The investigator considered all the listed events to be not related to quetiapine.
-

Clinical trials: patient narratives

- D1441C00089/0024/22004: (Case ID: 2005UW01522) 43-year-old female enrolled in an open label study. The patient was hospitalized on day 336 for severe prancreatitis. Initially admitted for symptoms of kidney stones. The patient had a nine-day history of abdominal pain and physical exam showed mildly distended abdomen with diffuse, bilateral quadrant tenderness. A CT scan of abdomen and pelvis showed inflammation and edema surrounding pancreas consistent with pancreatitis. The patient denied alcohol use although family stated that she might drink alcohol more than she is admitting to. Gallstone exam showed sludge in gallbladder. Amylase (54 no units) & lipase (37 no units) was within normal limits. The patient then developed fever and SOB and started on IV fluids. Chest x-ray showed pulmonary interstitial infiltrates in hilar location and upper lobes. CT showed interstitial infiltrates which was suspected of being PCP. An HIV serology was performed and was non reactive. Pancreatitis worsended. The patient was treated with antibiotics and recovered. SEROQUEL was discontinued. The investigator considered the event not related to SEROQUEL.



Clinical trials: patient narratives

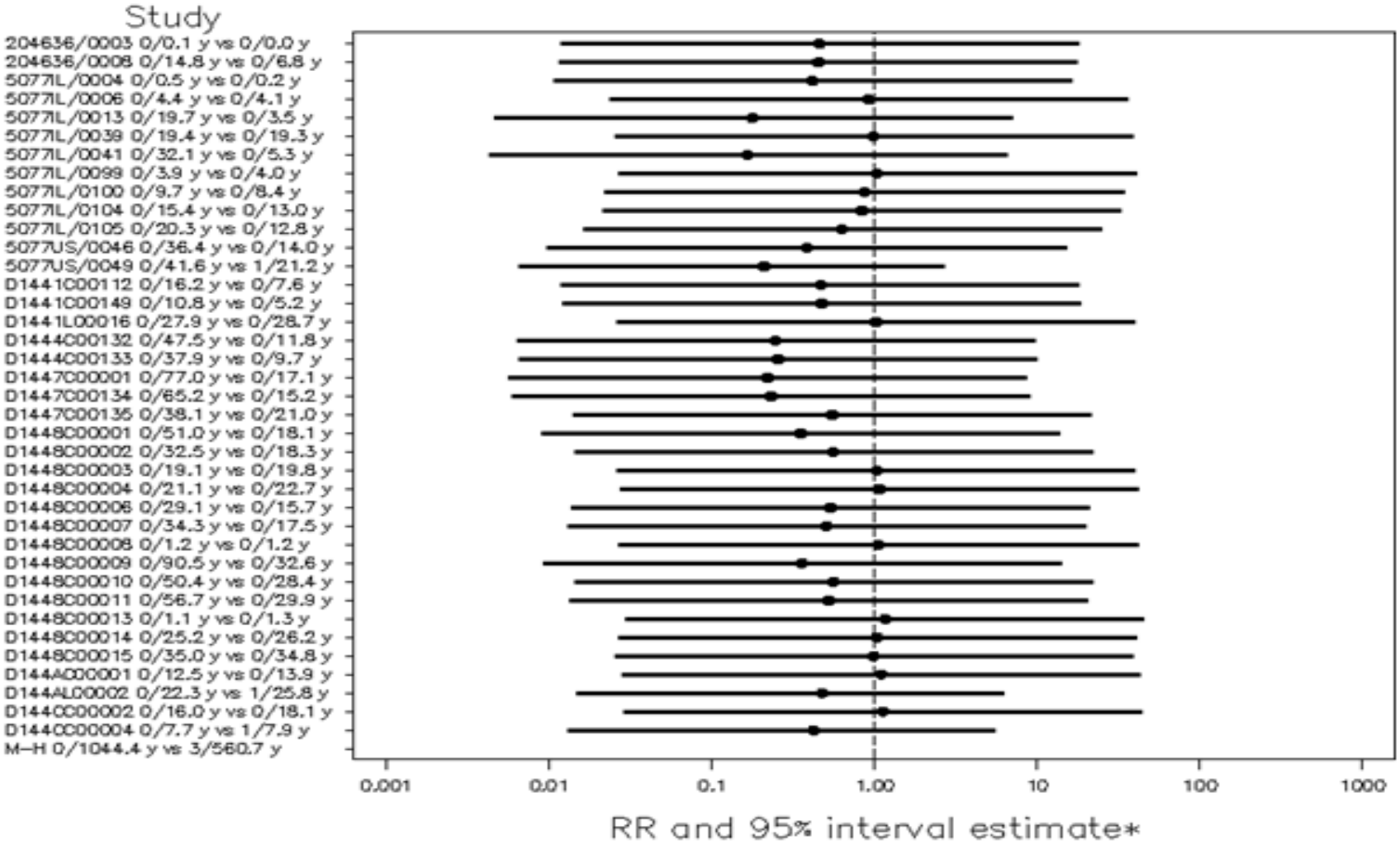
- 5077US/0043/0044/0135: 53-year-old female had a non-serious event of pancreatitis after 2 days on quetiapine, and recovered the next day. The patient was being treated with conjugated estrogens. The patient continued on quetiapine for 15 more days and thereafter was discontinued due to lack of efficacy. No amylase or lipase laboratory values were provided. The patient had relevant medical history of cholecystectomy and hysterectomy (relative timing is unknown). The event was considered related by the investigator.

Clinical trials: patient narratives

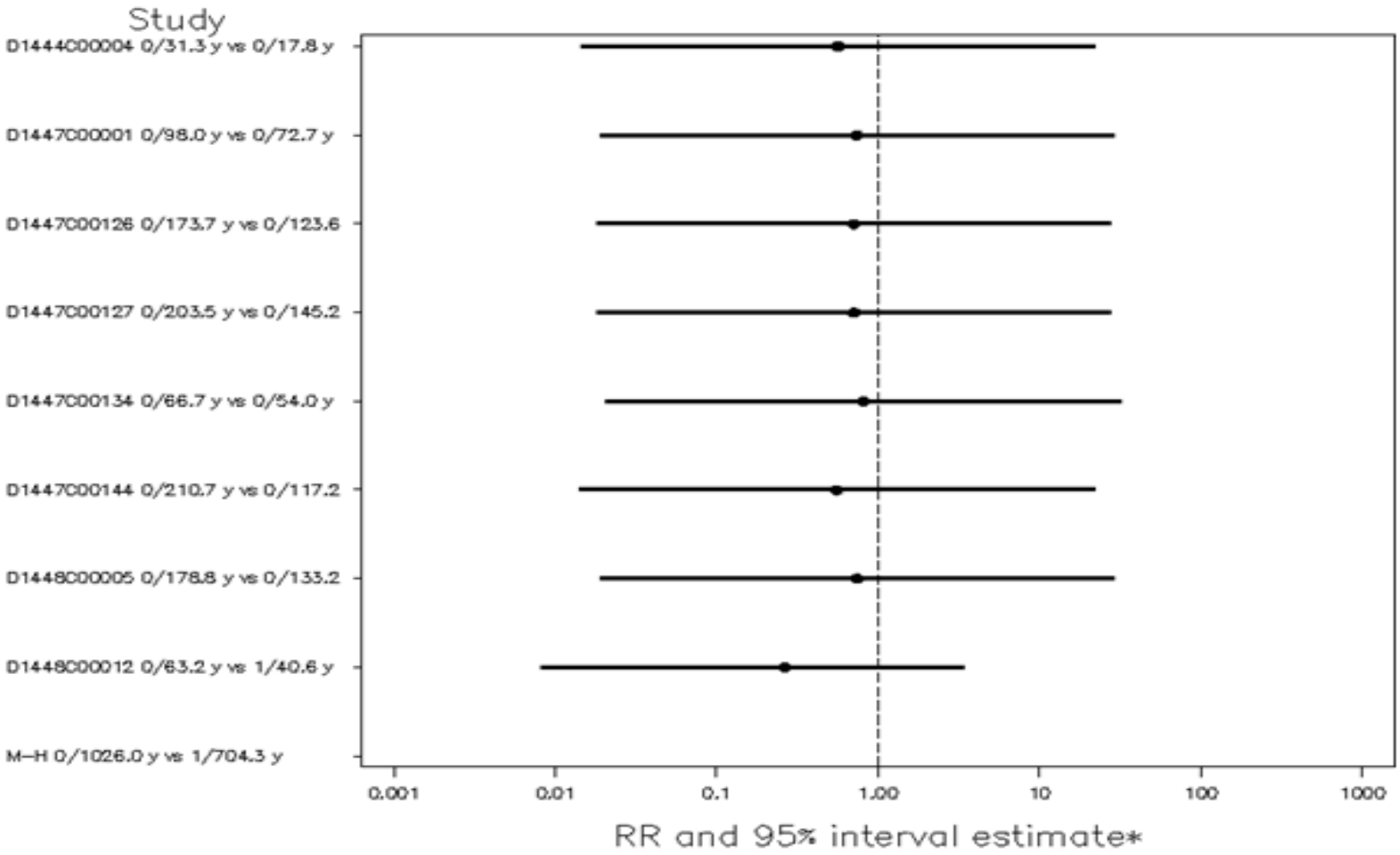
- 5077IL/0048/0008/0825: (case ID: 1997AP23269**)** 72-year-old male patient with psychosis who was also receiving enalapril, for which pancreatitis has been reported. The case did not provide any information on the three CIOMS criteria for acute pancreatitis of signs and symptoms, elevated enzymes levels of amylase or lipase, diagnostic procedures to confirm pancreatitis or the presence or absence of gallstones. The event was considered not related by the investigator. The event was initially reported as (Non- Serious) possible pancreatitis and then upgraded to (Serious) pancreatitis.



All Placebo-controlled trials



All long-term relapse prevention trials



Data Mining Terminology

- EBGM is the Empirical Bayes Geometric Mean - an adjusted estimate of the mean proportional reporting ratio that addresses small cell counts
  - EB05 = lower bound of confidence interval
  - EB95 = upper bound of confidence interval
- The widely used threshold for signal detection: EB05 >=2.



Some statistics …

- **Relative risk (RR)** is the ratio of the **probability** of an event occurring in an exposed group (treatment) to the probability of the event occurring in a non-exposed group (Placebo)

  - A relative risk of 1 means there is no difference in risk between the two groups.
  - An RR of < 1 means the event is less likely to occur in the treatment group than in the control group.
  - An RR of > 1 means the event is more likely to occur in the treatment group than in the control group.

- **MH RR**: Cochran-Mantel-Haenszel method is used to generate RR after adjusting for confounding factors (eg., stratified by studies)



Some statistics…

- Incidence rate : the number of new cases per population at risk in a given time period, it is also known as the **incidence** density **rate**

- MH incidence rate : number of new cases (per 100 patient - years in this case) after adjusting confounding factors with Cochran-Mantel-Haenszel method



Rule of 3

- In statistical analysis, the **rule of three** states that if a certain event did not occur in a sample with *n* subjects, 0 to 3/*n* is a 95% confidence interval for the rate of occurrences in the population. When *n* is greater than 30, this is a good approximation to results from more sensitive tests

- For example, in this case, 0 QTP patients had pancreatic event, the 95% confidence interval for the occurrence in QTP population is 0 to 3/2043 (~0.0015)



CIOMS criteria for diagnosis of pancreatitis

- Upper abdominal pain, which is severe and sudden, usually accompanied by vomiting, and in more severe cases by abdominal guarding, rigidity, rebound tenderness and diminution or loss of bowel sounds AND
- Increased pancreatic enzymes in the blood (amylase and lipase). Lipase is more specific than amylase, but an increase in either enzyme to at least twice the level of normal is significant.
- Confirmatory investigations: Whenever possible, the diagnosis should be confirmed by ultrasonography, computerized tomography (CT), or other imaging techniques.



Time and dose relationship

- Of the 156 medically confirmed reports, 104 reports did not provided any information regarding time to onset.
- Doses ranging from **50** mg to **1900** mg per day at the time of the pancreatitis event.
- There were 6 patients with a TTO ranging from **0** to 14 days, 6 for 15-30 days, 7 for 31-60 days, 3 for 61-120, 6 for 121-80, 5 for 181-365 and 18 for greater than **366** days.