

ATYPICAL ANTI-PSYCHOTICS AND THE RISK OF ACUTE KIDNEY INJURY

Dr.Faiq Unnisa, Dr. Aliya Parveen., Dr. Rukhaiya Fatima., Dr. Mehraj Unnisa., Sushma Attuluri & Abdul Saleem Mohammad

Department of Pharma.D, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

Student, Indiana Polis University IUPUI Indiana Polis, Indiana, United States.

Clinical Pharmacist, Virinchi Hospitals, Banjara Hills, Hyderabad, Telangana, India.

Department of Pharmacology, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

Department of Pharmaceutical Analysis and Quality Assurance, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

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ABSTRACT

Drug toxicity remains an important cause of acute kidney injury that, in many circumstances, can be prevented or at least minimized by vigilance and early intervention. Atypical antipsychotic medications are linked to acute kidney injury (AKI) in elderly patients, new research suggests, causing investigators to call for their use in this population to be reevaluated. Millions of adults worldwide are prescribed atypical antipsychotics every year. These drugs are frequently used to manage behavioral symptoms of dementia, which is not an approved indication, and such use has raised safety concerns. These medications antagonize alpha-adrenergic, muscarinic, serotonin, and dopamine receptors. AKI, or a sudden loss of kidney function, has been linked to use of these drugs in several case reports. Current evidence calls for a careful reevaluation of the prescribing of these medications in older adults. Physicians should be aware of the potential for atypical antipsychotics toxicity. It is important to consider all other options before going to these drugs. Change the environment, so it's not as agitating for the person. The drugs should be used only after other approaches have been exhausted; when prescribed, patients must be warned about potential adverse effects and proactive clinical monitoring shortly after initiation seems reasonable. The review suggests that atypical antipsychotics are hard on aging kidneys hence should be avoided in elderly patients with dementia as far as possible. The presence of retrospective database studies, and relevant published data from clinical trials, makes it easy to draw conclusions concerning risk for atypical antipsychotics in elderly.

Keywords: acute kidney injury, atypical antipsychotics, dementia, toxicity, clinical monitoring.

INTRODUCTION

Millions of adults worldwide are prescribed atypical antipsychotics every year. These drugs are frequently used to manage behavioral symptoms of dementia, which is not an approved indication, and such use has raised safety concerns. AKI, or a sudden loss of kidney function, has been linked to use of these drugs in several case reports.

The atypical antipsychotics quetiapine (Seroquel), risperidone (Risperdal), and olanzapine (Zyprexa)—commonly prescribed off-label to help manage behavioral symptoms of dementia—are associated with increased risk of acute kidney injury in older adults.

Fig no.1[1]

Atypical Antipsychotics Approved Products

Approved Products	Company	US Launch Year	2007 US Revenue (\$MM)	2007 US Y-o-Y Growth
Seroquel®	AstraZeneca	1997	3,256	13.2%
Risperdal®	J&J	1994	3,122	11.3%
Zyprexa®	Eli Lilly	1996	2,686	0.4%
Abilify®	BMS/Otsuka	2002	2,198	24.0%
Geodon®	Pfizer	2001	850	20.7%
clozapine	Novartis, others	1990	178	0.0%
Invega®	J&J	2007	75	-

CONFIDENTIAL

Source: IMS HEALTH National Sales Perspectives (2007), Vanda calculations



Fig no.2 [2]

MECHANISM OF ACTION

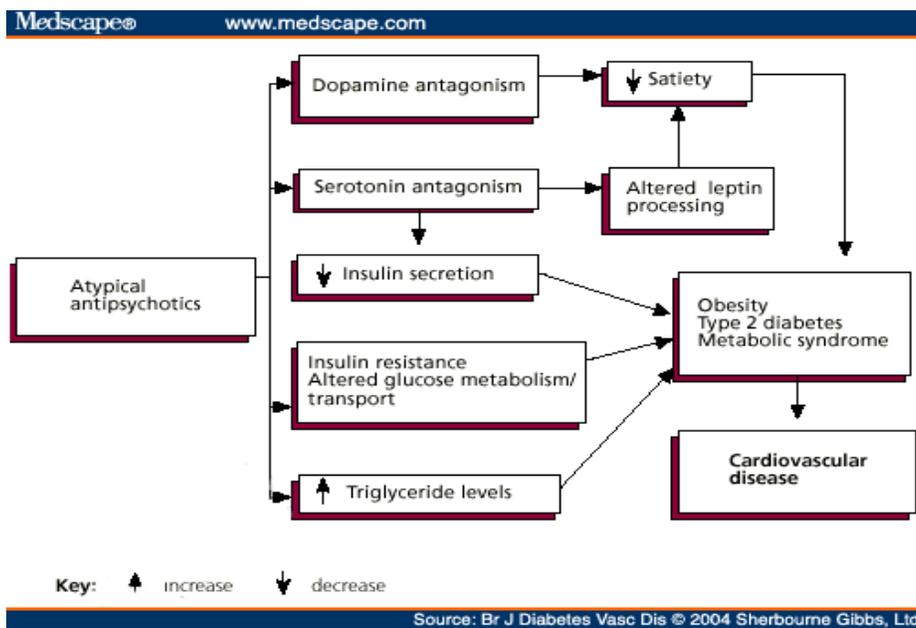


Table no.1[3]

SIDE EFFECTS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS

Side effects of Second Generation AntiPsychotics	Drugs most likely to least likely to have these effects
Weight gain,Diabetes	Clozapine > Olanzapine > Risperidone
Movement effects (eg : tremors , stiffness, agitation)	Risperidone > Olazapine > Clozapine
Sedation (eg: sleepiness, low energy)	Clozapine > Olanzapine > Risperidone
Decreased sex drive and function,missed periods, discharge from breasts	Risperodone > Olanzapine > Clozapine

Table no.2[4]

Metabolic effects : Comparison of Antipsychotics

MEDICATION	WEIGHT GAIN	RISK FOR DIABETES	WORSENING LIPID PROFILE
Clozapine	+++	+	+
Risperidone	++	+	+
Olanzapine	+++	D	D
Quetiapine	++	D	D
Ziprasidone*	+/-	-	-
Aripiprazole*	+/-	-	-

*Newer drugs with long term-data; +=increased effect; -=no effect; D=discrepant results

Table no.3[5]

TABLE
RECEPTOR BLOCKADE AND ANTIPSYCHOTIC SIDE EFFECTS²

Receptor Type Side Effects

D ₂	EPS, prolactin elevation
M ₁	Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision
H ₁	Sedation, weight gain, dizziness
α ₁	Hypotension
5-HT _{2A}	Anti-EPS (?)
5-HT _{2C}	Satiety blockade

D=dopamine; EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

Robinson DS. *Primary Psychiatry*. Vol 14, No 10. 2007.

Quetiapine is a dopamine, serotonin, and adrenergic antagonist, and a potent antihistamine with clinically negligible anticholinergic properties.

Mode of Action: D2,5-HT2,5-HT6,H1,α1,α2

- 1) Sedative
- 2) Anxiolytic
- 3) Antimanic
- 4) Mood stabilizing
- 5) Antidepressant

Fig no.3

Quetiapine antagonizing different receptors

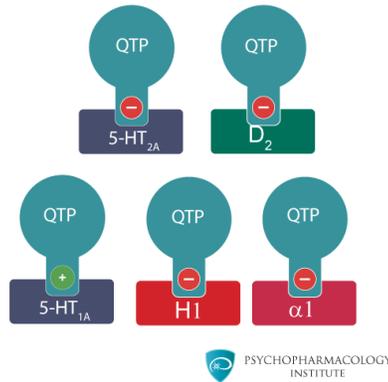
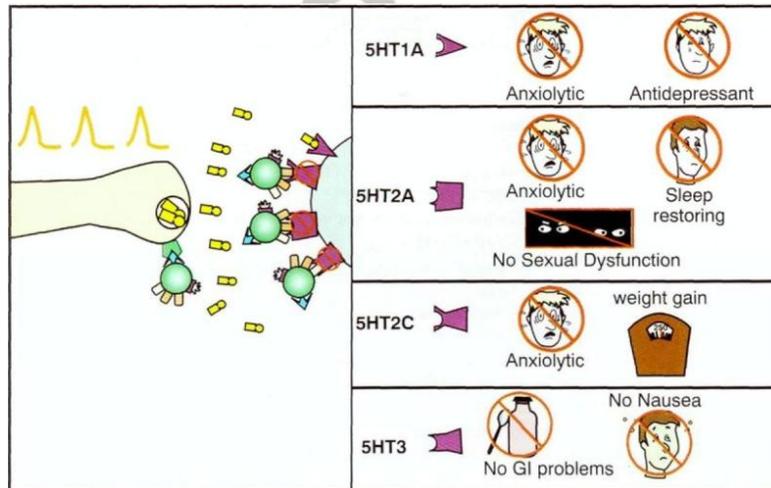


Figure no.4

Quetiapine(Seroquel)



Figure no.5 Quetiapine binding and its effects



Adverse effects :

Very common (>10% incidence) - dry mouth, dizziness, headache, somnolence (drowsiness).

Common (1-10% incidence) - high blood pressure, orthostatic hypotension, high pulse rate, high blood cholesterol, increased appetite, vomiting, increased liver enzymes, insomnia.

Rare (<1% incidence) - sudden cardiac death, syncope, diabetic ketoacidosis, hyponatraemia, low blood

sodium, leukopenia, a drop in white blood cell count, not as severe as agranulocytosis, suicidal ideation, priapism, tardive Dyskinesia.

Risperidone is a second-generation atypical antipsychotic. It is a dopamine antagonist possessing anti-serotonergic, anti-adrenergic and anti-histaminergic properties. It has actions at several 5-HT (serotonin) receptor subtypes.

1) 5-HT_{2C}- weight gain

2) 5-HT_{2A}- Antipsychotic action and relief of some of the extrapyramidal

side effects experienced with the typical neuroleptics.

Fig no.6 Risperidone antagonizing diferent receptors

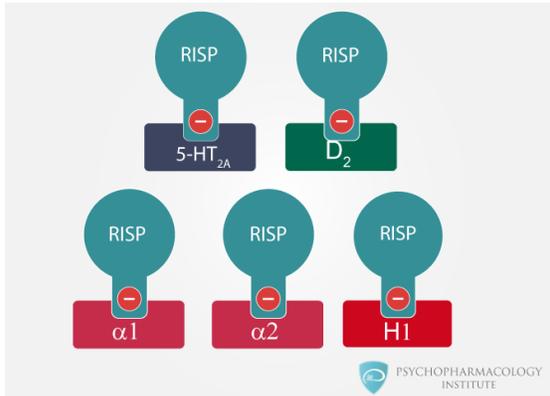
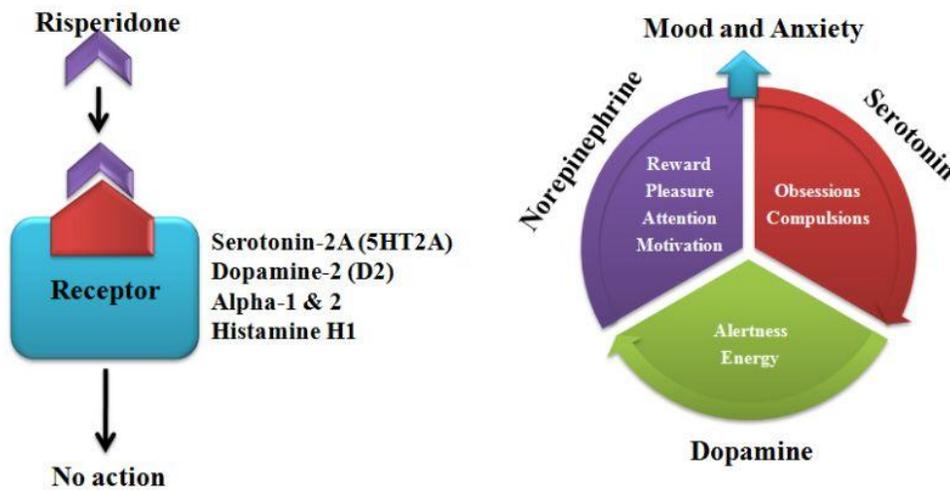


Fig no.7 Risperidone(Risperdal)



Fig no.8[6]

Risperidone (An antagonist drug, that binds with serotonin-2A (5HT2A), dopamine-2 (D2), alpha-1 & 2 and histamine H1 receptor).



Risperidone after binding with receptor does not provoke the biological response (Mood and Anxiety), but blocks the dopamine, serotonin, norepinephrine and histamine mediated responses.

Adverse effects:

Adverse effects of risperidone include significant weight gain and metabolic problems.

Common ($\geq 1\%$) - rash ,hyper prolactin aemia ,weight gain,constipation ,diarrhea, excessive Salivation , Increased appetite , indigestion, nausea, vomiting, upper abdominal pain , xerostomia, akathisia, dizziness ,dyspnoea asthenia , agitation ,urinary incontinence, arthralgia, myalgia, epistaxis, somnolence ,sleep disturbances ,dose-dependent extrapyramidal side effects such as dystonia and Parkinsonism ,nasal congestion nasopharyngitis,pain in the throat ,upper respiratory tract, fatigue, generalised pains,galactorrhea.

Rare - sudden cardiac death ,syncope ,diabetic ketoacidosis, pancreatitis, agranulocytosis , leucopenia, stroke,seizure tardive dyskinesia ,priapism ,pulmonary embolism , hyponatraemia.

Risperidone and other antipsychotics also increase the risk of death in people with dementia.

While antipsychotic medications such as risperidone have a slight benefit in people with dementia, they have been linked to higher incidences of death and stroke.Because of this increased risk of death, treatment of dementia-related

psychosis with risperidone is not FDA approved.

Older people with dementia-related psychosis are at a higher risk of death if they take risperidone compared to those who do not.

DOSAGE:

Risperidone is available as an oral tablet, oral dissolving tablet, or intramuscular injection.The intramuscular preparation, marketed as Risperdal Consta, can be given once every two weeks. It is slowly released from the injection site. This method of administration may be used on sanctioned patients (detained), who are refusing, or consenting patients who may have disorganized thinking and cannot remember to take their daily doses.

Olanzapine is an atypical antipsychotic that belongs to thienobenzodiazepine class. Olanzapine has a higher affinity for 5-HT_{2A} serotonin receptors than D₂ dopamine receptors.

In common with other second generation (atypical) antipsychotics, olanzapine poses a relatively low risk of extra pyramidal side effects including TD, due to its high affinity for the D₁ receptor over the D₂ receptor.

There are some case reports of olanzapine-induced diabetic keto acidosis.

Table no.4 OLANZAPINE ANTAGONISM AND ITS EFFECTS

ANTAGONISM	EFFECTS
Muscarinic M3 receptors	Diabetogenic effects
Dopamine receptors	Extrapyramidal effects and Therapeutic effects
Muscarinic Ach receptors	Dry mouth and Constipation
5-HT _{2C} and D ₂ receptors	Weight gain and appetite stimulation
H ₁ histamine receptors	Sedation and weight gain

Fig no.9 Olanzapine antagonizing different receptors

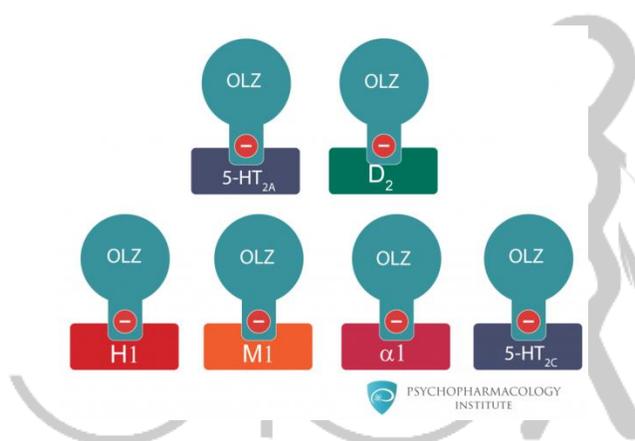


Fig no.10 Olanzapine(Zyprexa)



Adverse effects:

Very common (>10% incidence) -weight gain (dose-dependent), somnolence (dose-dependent), hyper prolactinemia , hypertriglyceridaemia.

Common (1-10% incidence) –Extra pyramidal symptoms (EPS) (dose-dependent),weight gain, Glucosuria ,orthostatic hypotension ,akathisia parkinsonism.

Uncommon (0.1-1% incidence) – leukopaenia,neutropaenia ,bradycardia , photosensitivity reaction, alopecia ,urinary incontinence ,urinary retention.

Rare (0.01-0.1% incidence) –hepatitis ,rash ,seizures.

Very rare (<0.01% incidence) – agranulocytosis ,thrombocytopenia, thrombo embolism, rhabdomyolysis, priapism ,urinary hesitation ,pancreatitis ,Neuroleptic malignant syndrome ,Jaundice ,diabetic coma,diabetic ketoacidosis ,type II diabetes mellitus ,sudden cardiac death ,anaphylactic reaction.

Acute kidney injury (AKI), previously called acute renal failure (ARF), is an abrupt loss of kidney function that develops within 7 days. Its causes are numerous.

AKI may lead to a number of complications, including metabolic acidosis, high potassium levels, uremia, changes in body fluid balance, and

effects to other organ systems. Management includes supportive care, such as renal replacement therapy, as well as treatment of the underlying disorder.

Fig no.11

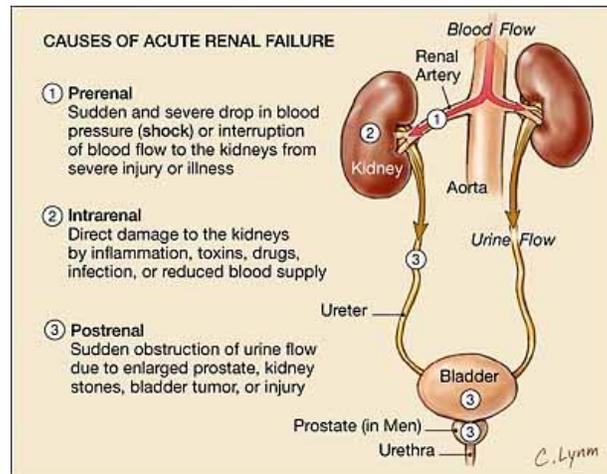


Fig no.12 Pathophysiology of AKI

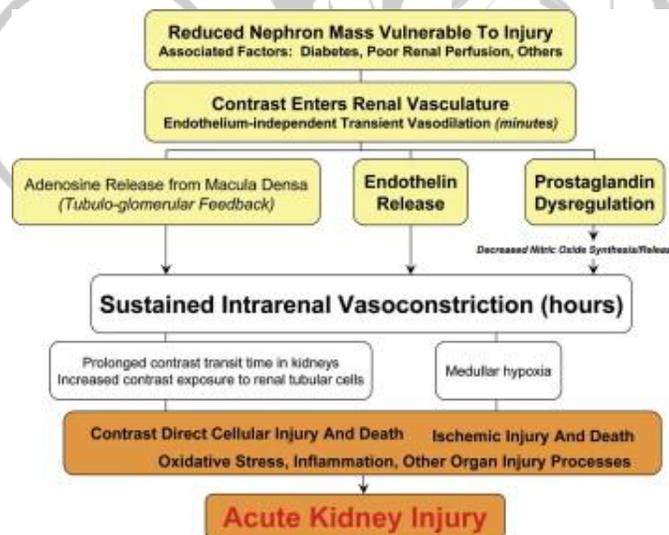


Fig no.13 Complications

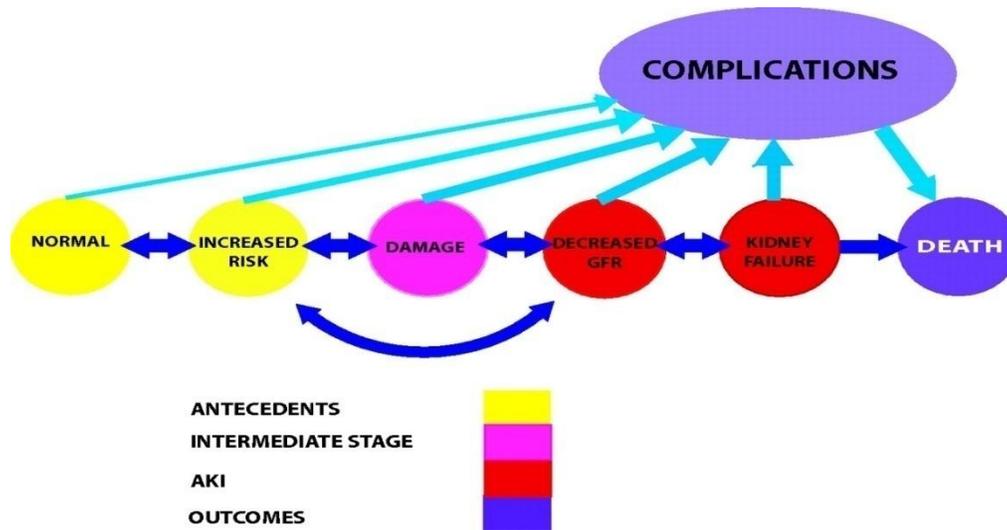
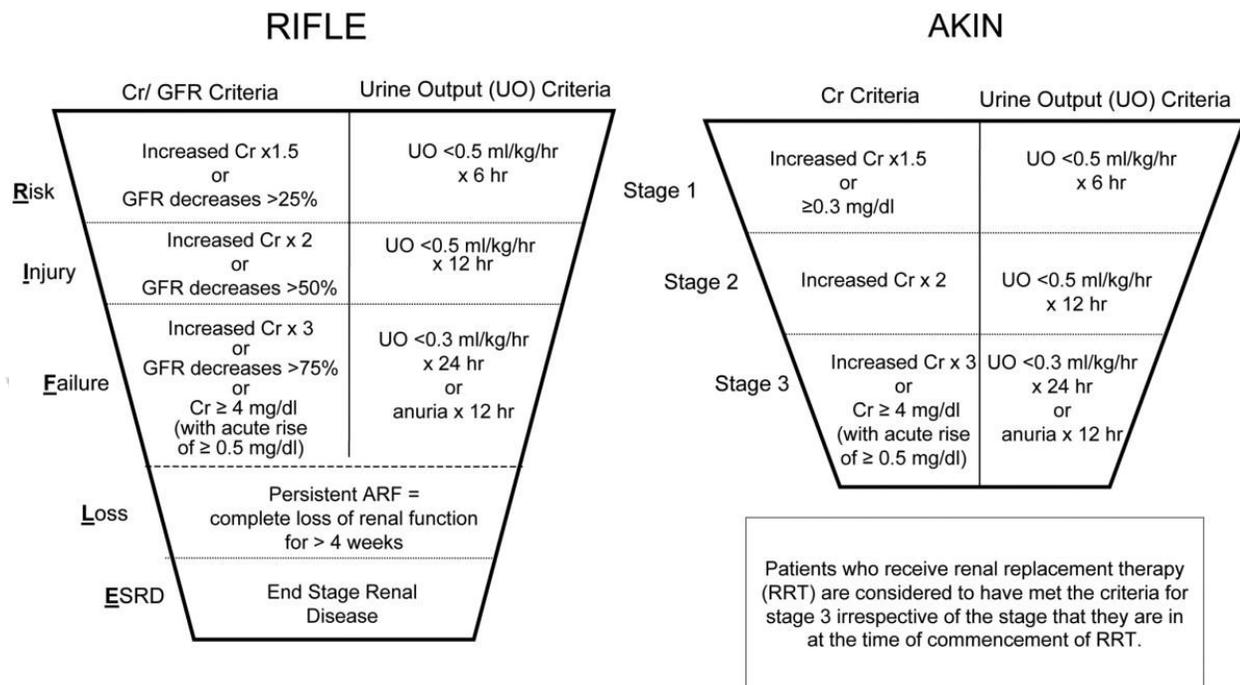


Fig no.14 DETECTING ACUTE KIDNEY INJURY:



ATYPICAL ANTIPSYCHOTIC'S ASSOCIATION WITH ACUTE KIDNEY INJURY:

❖ The study, done by researchers at the Lawson Health Research Institute in London, Ont., and the Institute for Clinical Evaluative Sciences, is the first to investigate the link between atypical antipsychotics and acute kidney injury.

Using Ontario health-care databases, researchers identified 97,777 patients 65 and older who were prescribed antipsychotic drugs between 2003 and 2011, and followed their health outcomes for 90 days. They compared the drug recipient group to the same number of

seniors who were not using the drugs. The mean age of both groups was 80.7 years. Within 90 days, 1,002 of those using atypical antipsychotics had been hospitalized with acute kidney injury, a sudden decline in kidney function that occurs in about 10 per cent of hospitalized patients. By comparison, only 602 of those not taking the drugs were diagnosed with acute kidney injury during the same 90-day period. This retrospective cohort study also found that atypical antipsychotic drug use was associated with a higher 90-day risk for hospitalization pneumonia, heart attack, ventricular arrhythmia, low blood pressure and inability to pass urine.[7]

- ❖ A population-based study examining medical records for nearly 200,000 adults older than 64 years showed that those who received a prescription for quetiapine (Seroquel, AstraZeneca Pharmaceuticals LP), risperidone (Risperdal, Janssen Pharmaceuticals, Inc), or olanzapine had an almost 2-fold increased risk for hospitalization for AKI within the next 90 days vs those who did not receive these prescriptions.

In addition, patients who received 1 of these oral atypical antipsychotics had increased risk for acute urinary retention, hypotension, and even death.

"This shows that use of these medications was associated with a higher risk of being hospitalized for kidney injury, as well as other adverse outcomes that might explain the reasons why people get kidney injuries," principal investigator Amit X. Garg,

MD, PhD, kidney specialist at the London Health Sciences Center and from the London Kidney Clinical Research Unit in Ontario, Canada, told Medscape Medical News.[8]

- ❖ The new study confirmed those findings. During the 90-day study period, 6,666 of the drug recipients died from all causes, compared to just 2,985 non-recipients.

"That's a lot of extra, additional deaths that may not have occurred," said Garg, who called the increase in all-cause mortality "a pretty robust signal. The warnings are out there and yet these drugs are still commonly prescribed." The study's findings don't apply to younger patients prescribed the drugs to control psychosis, Garg said. They are less prone to adverse drug events than the elderly, who metabolize drugs more slowly and have fewer reserves in their kidneys and other organs, he said.

- ❖ The Federal Drug Agency (FDA) has issued a black box warning for these drugs based on 17 trials that demonstrated an increased rate of death in elderly patients with dementia taking these drugs.

This population-based retrospective cohort study sought to examine the risk of hospitalization secondary to acute kidney injury (AKI) and other adverse outcomes associated with new oral atypical antipsychotic use in the elderly. The study included residents of Ontario, Canada aged older than 65 years who received a

new prescription for atypical antipsychotics in the non-hospital setting. Patients that received these drugs, when compared to untreated matched controls, were at significantly increased risk of hospitalization for acute kidney injury (AKI).

The results also suggested an association between atypical antipsychotic use and other complications including hypotension, acute urinary retention, pneumonia, acute myocardial infarction and ventricular arrhythmia.

Furthermore, subjects that were taking these drugs were over twice as likely to die from any cause during the 90-day follow-up period.

A major weakness of this study was the limited study population, as well as the failure to identify and include patients who experienced AKI without hospitalization as a study outcome.[9]

Based on randomized trials, the U.S. Food and Drug Administration has warned of an increase risk of death in older patients treated with the drugs.

Atypical antipsychotics given to elderly patients in outpatient setting were associated with a 75% increased 90-day risk of hospitalization for acute kidney injury (AKI) when compared to untreated controls.

Older patients taking atypical antipsychotics were nearly twice as likely to develop multiple severe complications, including death.

For the study, the team examined routine clinical care and administration data from a UK primary care database, the Health Improvement Network. Specifically, they determined the proportion of individuals prescribed antipsychotics between 2007 and 2011 with a diagnosis of psychosis and bipolar disorder; other diagnoses, including depression, anxiety, and dementia; or none of these diagnoses. A total of 47,724 individuals were prescribed antipsychotic agents during the study period, including 13,941 who received first-generation drugs and 27,966 who were prescribed second-generation agents. The median length of follow-up was 2.4 years. Women were significantly more likely to be prescribed antipsychotics than men, at an incidence rate ratio (IRR) of 1.092. Prescribing rates were also significantly higher among older people, at an IRR for those aged more than 80 years vs those aged 40 to 49 years of 2.234. For second-generation antipsychotics, the proportion with an SMI (serious mental illness) diagnosis ranged from 36% for quetiapine (Seroquel, AstraZeneca Pharmaceuticals LP) to 62% for olanzapine (multiple brands). Among individuals with no SMI diagnosis, antipsychotics were most often prescribed for anxiety, depression, dementia, and sleep and personality disorders. The respective proportions for risperidone (Risperdal, Janssen Pharmaceuticals, Inc) were 14%, 22%, 12%, 11%, and 4%.[10]

CASE REPORTS:

Olanzapine and Acute Urinary Retention in 2 Geriatric patients:[11][12]

A report has been made to discuss the possibility that administration of olanzapine may provoke acute urinary retention (AUR) in some patients. Results include the development of AUR leading to acute renal failure subsequent to olanzapine administration in 2 geriatric patients with benign prostatic hypertrophy (BPH). Given the cases presented, we recommend that clinicians measure electrolytes, blood urea nitrogen, and creatinine every 2 or 3 days for 1 or 2 weeks after initiating olanzapine treatment and after each dose increase. This is especially important for cognitively impaired elderly patients with BPH, as they may not be able to provide clear feedback regarding adverse effects of the medication.

Table no.5 Overview of Reported Cases of Clozapine-Induced Renal Failure[13]

CASE REPORT	AGE/SEX	CLOZAPINE DOSING /d	RECHALLENGE?	MEDICATIONS AT TIME OF CLOZAPINE TREATMENT	TIME TO HYPERSENSITIVITY OR SYMPTOM ONSET	FEVER	RASH / ARTHRALGIA	ESINOPHILIA/CRP	MEDICATIONS ADDED AFTER SYMPTOMS ONSET	URINALYSIS	BIOPSY RESULT
Elias et,al 1999	38/Female	↑ Over 11 days to 250 mg/d	NR	Lithium, venlafaxine	11 days	NR	NR	NR	Hemodialysis	Anuric on admission	Acute interstitial nephritis
Fraser and Jibani 2000	49/Male	NR	Yes, during same admission	Flupenthixol IM (on admission), mianserin hydrochloride (on admission), thioridazine added (not clear if these 3 medications were stopped prior to clozapine), diazepam prn	10 days after first trial; 2 days after rechallenge	Yes	NR	NR	IV cefotaxime, dopamine, and furosemide infusions; peritoneal dialysis; IV methyl-prednisolone and po prednisone for acute interstitial nephritis; hemodialysis	NR	Acute interstitial nephritis
Southhall 2000	24/Female	↑ Over 8 days to 300 mg/d	NR	NR	8days	Yes	NR	↑ Eosinophilia (0.54 × E9/L) ↑ CRP (58 mg/L)	NR	Proteinuria, many WBCs, many RBCs	Not done
Estebanez et.al 2002	69/Male	NR	NR	Valproic acid, trihexyphenidyl	After 3 months, the patient was	NR	NR	NR	IV prednisone	Proteinuria, 1-3 WBC/HPF	Acute interstitial nephritis

					discovered to be in acute renal failure						
Au et.al 2004	33/Male	25 mg titrated to 100 mg/d	NR	Valproic acid, gabapentin, risperidone	1 week	Yes	NR	↑ Eosinophilia (6.1%)	Trimethoprim	Proteinuria, WBCs	Not done; ultrasound: glomerular nephritis
Siddiqui et al 2008	26/Male	Titrated up to 125 mg/d	NR	Valproic acid, lithium, risperidone, clonazepam; patient was gradually switched from risperidone to clozapine	2 weeks	Yes	NR	↑ Eosinophilia (820/mm ³)	IV steroids	Proteinuria, 5–10 WBC/HPF	Not done
Hunter et al, 2009 ⁷	57/Female	12.5 ↑ to 25 mg/d (5 doses)	Yes, 4 years later	Olanzapine, sodium valproate, IM haloperidol, levomepromazine (discontinued before clozapine)	<1day	Yes	NR	↑ CRP (197 mg/L)	Trimethoprim, amoxicillin	Proteinuria and RBCs, then WBCs but no RBCs	Not done
Kanofsky et al, 2011	28/Male	12.5 mg titrated to 125 mg/d	NR	Lithium, divalproex, haloperidol, perphenazine, benztropine	7days	Yes	No	↑ Eosinophilia (8%) 12 days after clozapine	Acetaminophen, IV ketorolac, levofloxacin, moxifloxacin, prednisone for acute renal failure	RBCs	

Abbreviations: CRP = C-reactive protein, HPF = high power field, IM = intramuscular, IV = intravenous, RBC = red blood cell, WBC = white blood cell, NR= None Reported Symbol: ↑ = increased or elevated.

ATYPICAL ANTIPSYCHOTICS FOR DEMENTIA? ^[14]

Though antipsychotics are widely used to control behaviours associated with dementia, that is not an approved use for the drugs and has become increasingly controversial.

Earlier this summer, the Royal Ottawa Health Care Group announced its involvement in a project aimed at reducing the use of antipsychotic drugs at the Peter D. Clark Long Term Care Home.

For dementia patients, “you can do many things before you have to turn to these

drugs,” Garg said. For example, “you can control the environment in better ways so that the person doesn’t get agitated.”

“We wanted to raise awareness around this issue and recommend that physicians should be cautious around the use of these medications in the elderly,” said Dr. Garg.

“However, if a patient is on this medication and the physician is monitoring it very carefully, we don’t want to be alarmists. But it’s healthy to have these types of conversations.”

DOSE RECOMMENDATIONS:

Table no.6[15]

SUGGESTED DOSES OF ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH DEMENTIA-

DRUG	STARTING DOSE	TARGET DOSE
Aripiprazole	2-5 mg/d	7.5-12.5 mg/d
Olanzapine	2.5-5 mg/d	5-10 mg/d
Quetiapine	12.5-25 mg/d	50-200 mg/d
Risperidone	0.25-0.5 mg/d	0.5-1.5 mg/d

Table no.7[16]

MAXIMUM RECOMMENDED ANTIPSYCHOTIC DOSES FOR BPSD-

ATYPICAL ANTIPSYCHOTICS	MAXIMUM DAILY DOSE
Aripiprazole	10 mg
Clozapine	50 mg
Olanzapine	5 mg
Quetiapine	150 mg
Risperidone	2 mg

BPSD-Behavioural and Psychological Symptoms Of Dementia

CONCLUSION:

There are a number of possible explanations for the high rates of antipsychotic prescribing to people without a psychosis diagnosis. First, it may be that the clinician prescribes antipsychotics because the person does have psychotic symptoms, but the clinician does not assign a label of schizophrenia or other psychosis, either due to patient preference or to avoid the associated stigma with such labels. However, this would suggest that there are large numbers of people with unrecorded psychosis and/or bipolar disorder in primary care. They are often older people with conditions including dementia, non-psychotic depression, anxiety and sleep disorders. Although antipsychotics may be used in sleep disorders, treatment guidelines do not recommend using such agents on account of their side effect profiles. These agents are more commonly prescribed to older people, despite the propensity of this age group to develop side effects. Antipsychotics are still commonly prescribed to people with a diagnosis of dementia, contrary to clinical guidance, and this needs further attention.

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