Pharmacy Drug Class Review

July 16, 2009

Disclaimer: Specific agents may have variations

Atypical Antipsychotics and Metabolic Effects

Special literature review in conjunction with UB's APPE Student: Joe Steblein Pharm.D. Candidate 2009

Highlights: The Quick-Read Information **Link to Answer Key**

1. Which 2 atypical antipsychotics are associated with the MOST weight gain, risk of diabetes, worsening lipid effects?
   a. [Aripiprazole, Ziprasidone]; b. [Risperidone, Quetiapine]; c. [Clozapine, Olanzapine]
2. True or False, ADA guidelines on testing of baseline glucose and lipids are adhered to at similar rates regardless of patient age?
   a. [True]; b. [False]
3. Which 2 atypical antipyschotics have demonstrated weight LOSS?
   a. [Aripiprazole, Ziprasidone]; b. [Risperidone, Quetiapine]; c. [Clozapine, Olanzapine]
4. Which atypical antipsychotic, recently approved is the major active metabolite of a previously approved antipsychotic drug?
   a. [risperidone]; b. [aripiprazole]; c. [paliperidone]; d. [ziprasidone]
5. Which atypical antipsychotic is 1 of only 2 BRAND NAME atypicals on IHA's Tier 2 formulary?
   a. [Invega]; b. [Abilify]; c. [Risperdal regular tabs] d. [Abilify Discmelt]

- The various atypical antipsychotics have different binding affinities for various chemical receptors which appear to determine their efficacy AND their contributions to weight gain, glucose dysregulation and other significant adverse effects.
- Unfortunately, there seems to be a positive correlation between atypical antipsychotic efficacy and worsening metabolic effects.
  - In apparent contrast to above correlation, recent trial FIN11 published in *The Lancet*, showed substantially LOWER mortality with clozapine vs. any other antipsychotic (of those tested).
- The ADA released guidelines (2004) for baseline glucose and lipid testing for those starting atypical antipsychotics. Following release of these guidelines testing was increased but remained substantially LOW with LESS than 1 in 4 patients getting baseline glucose testing and about 1 in 10 patients getting baseline lipid testing. Testing increased with age; however this is more likely due to increased testing due to age and relation to risk of diabetes, hyperlipidemia etc NOT because physicians were testing more with atypical antipsychotic drug initiations.
  - Metabolic effects of atypical antipsychotics do NOT discriminate based on age, thus we MUST improve testing especially with younger patients initiating atypical antipsychotics.

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Generic (Trade)	FDA-Approved Indications	OFF-label Uses	Available Strengths/ Formulations	Significant or Unique ADRs[§] or Misc Notes	Administration Notes	Formulary Info* IHA
Clozapine (Clozaril®) *FazaClo (ODT)*	Schizophrenia Shizoaffective disorder	Agitation Bipolar disorder Dementia Tremor Parkinson's	Brand: 25, 100 mg Generic: 25, 50, 100, 200 mg FazaClo (ODT): 12.5, 25, 100 mg	Agranulocytosis Neutropenia *Dose limits:* Adult – 900mg/d Elderly – 450mg/d Adolescent (≥9) – 200-300mg	Take w/ OR w/o food Not labeled for children	Brand: Tier 3 Generic: Tier 1 (PAR except psych)
Olanzapine (Zyprexa®) *Zydis® (ODT)*	Acute psychosis Agitation Bipolar disorder Mania Schizophrenia	Depression, dementia, adverse rxn to cannabis, anorexia, anxiety-dementia, cancer-nausea-pain, chemo n/v, delirium, trichotillomania	Brand: 2.5, 5, 7.5, 10, 15, 20 mg ODT: 5, 10, 15, 20 mg	*Dose limits:* Adult/elderly – 20 mg po/day, 30 mg IM/day Adolescents (and ≥6) – 20 mg po/day	Take w/ OR w/o food Not labeled for children	Brand only: Tier 3 (PAR except psych) Zydis ODT: Tier 3 (PAR except psych)
Quetiapine (Seroquel®) also XR	Bipolar disorder Depression Mania Schizophrenia	Agitation, Dementia, OCD, Parkinson's, Delirium	Brand: 25, 50, 100, 200, 300, 400 mg XR: 50, 150, 200, 300, 400 mg	*Dose limits:* Adult – 800 mg Elderly – 200 – 800 mg	Take XR w/o food or with light (300Kcal) meal Not labeled for children Has active metabolite	Brand only: Tier 3 (PAR except psych)
Risperidone (Risperdal®) *RisperdalConsta®* *M-tab (ODT)*	Autism Bipolar Disorder Mania Schizophrenia	Acute psychosis, agitation, ADHD, dementia, psychotic depression, OCD, Tourette's, Levadopa ADR, Stuttering	Brand/Generic: 0.25, 0.5, 1, 2, 3, 4 mg Consta: 12.5, 25. 37.5, 50 mg Soln: 1 mg/ml M-tab: 0.5, 1, 2, 3, 4 mg	Dose limits: Adult – 8 mg po/d, 50 mg IM/2wks (max clinical effect seen at 4 – 8 mg/d) Elderly – 4 mg po/d, 2 mg/d per OBRA unless documented Children – varies w/wt and use	Take w/ OR w/o food Used in children as young as 5 yrs(some indications) Has active metabolite Solution NOT compatible w/ Cola or Tea	Brand: Tier 3 Generic: Tier 1 (>2 mg – PAR ex/psych) Soln: (PAR ex/psych, Age ≤12 yrs only) **M-tab: Tier 2 (PAR)**
Aripiprazole (Abilify®) *Discmelt®*	Agitation Bipolar disorder Depression Mania Schizophrenia	Borderline personality disorder	Brand: Tab – 2.5,10,15,20,30 mg Soln – 1 mg/ml IM – 9.75 mg/1.3 ml	*Dose limits:* Adult/elderly – 30 mg po/d, 25 mg solution/d, 30 mg IM/d ≥10 yrs – 30 mg po/d	Take w/ OR w/o food Labeled for ≥10 yrs Has active metabolite	**Brand only:** **Tier 2** (PAR except psych) Discmelt – Tier 3
Ziprasidone (Geodon®)	Acute psychosis, Agitation, bipolar disorder, mania, psychotic depression, schizophrenia	Tourette's Schizoaffective disorder	Brand: 20, 40, 60, 80 mg	Signif QTc Prolongation *Dose limits:* Adult/elderly – 160 mg po/day, 40 mg IM/day	Take w/ OR w/o food	Brand only: Tier 3 (PAR except psych)
Haloperidol (Haldol®) *Also Decanoate*	Acute psychosis ADHD Schizophrenia Tourette's	Agitation, autism, delirium, dementia, mania, n/v, singlutus (hiccups)	Generic: Tab – 0.5, 1,2 5,10,20 mg IM deconoate – 50,100 mg	Signif QTc Prolongation *Dose limits:* Adult/elderly – 100 mg po/day, 450 mg IM/mth Adolescent – 100 mg/d, IM not estab Children 3-12 yrs, 15-40 kg 0.15 mg/kg	Take w/ food or full glass of water or milk to minimize GI irritation, Do NOT dilute concentrated soln w/ coffee or tea	Brand: Tier 3 Generic: Tier 1
Paliperidone (Invega®)	Schizophrenia	n/a	Oral tab ER: 3, 6, 9 mg	Max dose: 12 mg/day Significant Renal elimination	Major active metabolite of risperidone Take w/ OR w/o food	Brand only: Tier 3 (PAR except Psych)

***Current through June 2009; **Available generically; §ADRs = Adverse Drug Reactions; PAR = Prior Auth Req'd**

Points of Interest

INTRODUCTION

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Patients with psychiatric disorders die prematurely of coronary heart disease when compared to the general population due to an increased prevalence of metabolic disorders such as diabetes mellitus, hyperlipidemia, and obesity. Psychiatric illness typically leads to an increase in smoking, sedentary living, and poor dietary choices, each of which is a known risk factors for metabolic disorders. They cannot, however, account for all of the increased risk in these patients.

Atypical antipsychotics (AA) are FDA approved to treat schizophrenia, bipolar disorder, and autism, although they are often used off label to treat dementia, depression, acute psychosis, tourette syndrome, agitation, attention deficit hyperactivity disorder, and post traumatic stress disorder. They were developed to avoid the movement disorders caused by first generation antipsychotics known as extrapyramidal symptoms, but they came with their own side effects including hyperglycemia, weight gain, dyslipidemia, and impaired insulin sensitivity. Each of these adverse effects correlates with the development of the metabolic disorders that are common in psychiatric patients, which in turn adds to the risk of coronary heart disease and death.

Given the AAs contribution to psychiatric patients' morbidity and mortality, the American Diabetic Association developed guidelines for patients starting on AAs that recommend baseline and follow up monitoring of blood glucose and lipids. These blood tests not only help physicians prescribe the most appropriate atypical antipsychotic initially, but also signal when to switch to another atypical antipsychotic. A recent study, however, found that after the ADA guidelines were published in 2004, only a minority of patients prescribed AAs received blood tests.[1] Clinicians need to identify barriers to monitoring and develop methods to improve adherence to the ADA's guidelines.

BACKGROUND

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Atypical antipsychotics antagonize serotonin, dopamine, histamine, noradrenergic, and muscarinic receptors to a varying degree, which gives each agent a distinct pharmacologic profile. These pharmacodynamic differences largely predict the spectrum of adverse effects seen clinically. Table 1 lists the binding affinities (Ki) of the AAs for each receptor.[2]

Binding affinities may be important because weight gain is most closely affiliated with blockade of the H1 receptor; however the D2, 5-HT1a, and 5HT2c receptors may be involved. In addition, glucose dysregulation is most associated with a drug's affinity for the H1, M3, and 5HT2c receptors. The receptors most responsible for causing hyperlipidemia are less clear. Blockade of muscarinic receptors is known to cause dry mouth, blurry vision, and constipation. Alpha-1 receptor blockade leads to orthostatic hypotension and is also not affiliated with metabolic effects.[3]

Metabolic syndrome links obesity, diabetes, and hyperlipidemia together rather than think of them as distinct diseases. The adverse effects of the AAs may be thought of in similar fashion, as weight gain is a known factor in the development of diabetes and hyperlipidemia. Since the H1 receptor is most prognostic of weight gain, olanzapine and clozapine are PREDICTED to have the largest metabolic effects, while aripiprazole and ziprasidone the least. Unfortunately, there seems to a *tie between AA efficacy and metabolic effects*, as clozapine and olanzapine are the most efficacious agents. Clozapine is particularly valuable, as it is the drug of choice in treatment resistant schizophrenia, although it's severe adverse effect, agranulocytosis, limits its role to a third line agent.

	D_2	5-HT_{2A}	α_1	H_1	M_1
Aripiprazole	0.34*	3.4*	57	61*	>1,000
Clozapine	126	16	7	6	1.9
Haloperidol	0.7	45	6	440	>1,500
Olanzapine	11	4	19	7	1.9
Quetiapine	160	295	7	11	120
Risperidone	4	0.5	0.7	20	>10,000
Ziprasidone	5	0.4	11	50	>1,000

*Data represented as K_i (nM); *Data with cloned human receptors*
Abbreviations: D = dopamine, 5-HT = serotonin, α_1 = alpha-1 norepinephrine, H_1 = histamine 1, M_1 = muscarinic acetylcholine-1

TABLE 1

Note: The FIN11 Study, recently published in *The Lancet*, found that clozapine seemed to be associated with substantially LOWER mortality than ANY other antipsychotics (tested in study). It cannot be said this was due to efficacy of the drug alone. Clozapine carries strict restrictions and patients have significantly greater follow up via health professionals than any other given antipsychotic. These factors are likely significant contributors to the observed mortality difference.

Link to FIN11 Study

CLINICAL DATA

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A 10 week meta-analysis done by Allisone *et al.*[4] reported the largest weight gains with clozapine(4.45kg), and the smallest with ziprasidone(0.04kg), although quetiapine had insufficient data, and aripiprazole was not on the market yet.

Haddad *et al.*[5] conducted a 3-8 week placebo controlled trial of five atypical antipsychotics, and reported patients gaining more than 7% of baseline bodyweight. Results are shown in Figure 1. Olanzapine was the highest reported and aripiprazole the lowest. Also interesting is that every drug measured had more than double the weight gain when compared to placebo, even ziprasidone and aripiprazole.

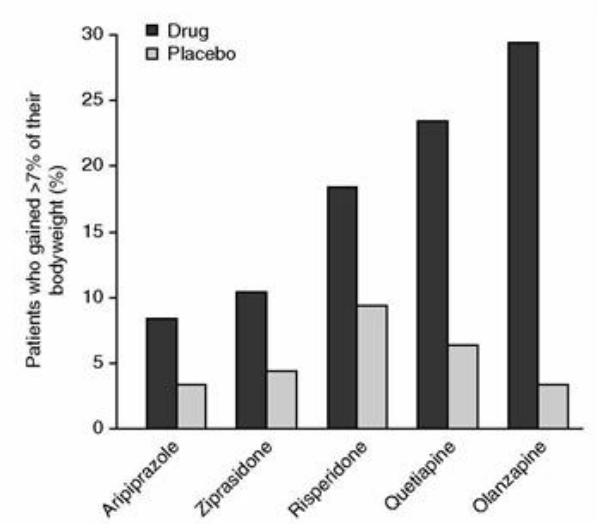


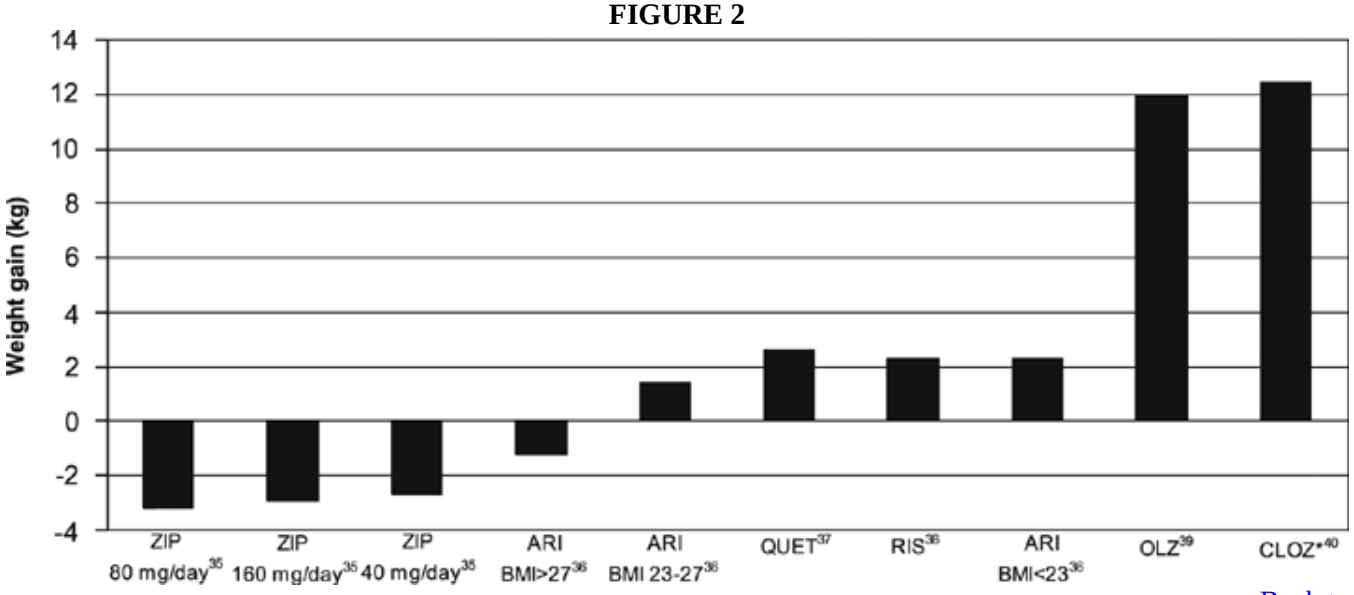
FIGURE 1

Graham *et al.*[6] reported that in patients with their first episode of psychosis, olanzapine caused a marked increase in central body fat deposition that is associated with raised triglyceride and insulin levels.

Long term studies on clozapine show steady increases in weight gain for 4 years, while studies olanzapine generally report the weight gain to plateau after 1 year, and risperidone has been reported to stabilize at 10 weeks.[7,8,5] Quetiapine appears to have mixed results, with some studies showing weight gain continuing after 1 year, while others show short term gains only.[9]

Figure 2 is a graph of one year weight gain after AA initiation featured in a review article by Narallah in Molecular Psychiatry.[3] At one year, olanzapine and clozapine are associated with weight gain far greater the other agents, while ziprasidone and one of the aripiprazole trials are actually associated with weight loss.

FIGURE 2



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One-year weight gain in patients treated with atypical antipsychotics. ZIP=ziprasidone, ARI=aripiprazole, QUET=quetiapine, RIS=risperidone, OLZ=olanzapine, CLOZ=clozapine, BMI=body mass index. *Denotes 10 month data.

Results from the CATIE trial[10], a large study to evaluate the effectiveness of typical and atypical antipsychotics, showed that discontinuation for olanzapine (9%) due to weight gain to be significant over discontinuation over all the other study medications (1-4%). On the other hand, olanzapine has the lowest rate of discontinuation due to a lack of efficacy (15% vs 24-28%) and the fewest hospital admissions due to relapse (11vs 15-20%). Additionally, a slightly higher amount of patients on ziprasidone and quetiapine required the highest doses allowed by the study compared to the other drugs.

ADA GUIDELINE

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The 2004 ADA guidelines recommend baseline and follow up monitoring for any patient starting on an AA, table 2 highlights the recommendations.[11] Baseline should include personal/family history, weight(BMI), waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile. The fasting lipid profile should be repeated at 12 weeks, and if there is little change from baseline, then every 5 years. Fasting plasma glucose is recommend to be tested at 12 weeks and then annually, while weight should be measure every 4 weeks up to 12 weeks, then four times a year.

TABLE 2

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

Table 3 is 2004 ADA guidelines assessment of the metabolic risks of each AA, with the greatest risk assigned to clozapine and olanzapine and the smallest risk assigned to ziprasidone and aripiprazole. If a patient develops diabetes, worsening dyslipidemia, or significant weight gain, clinicians are advised to switch a patient to an antipsychotic with less potential for metabolic side effects, and patients should be referred to a specialist for diabetes care. Immediate care, however, is required for those with symptomatic hyperglycemia, severe hyperglycemia (>300mg/dl), symptomatic hypoglycemia, blood glucose less than or equal to 60mg/dl, or symptoms of diabetic ketoacidosis.

TABLE 3

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

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TESTING

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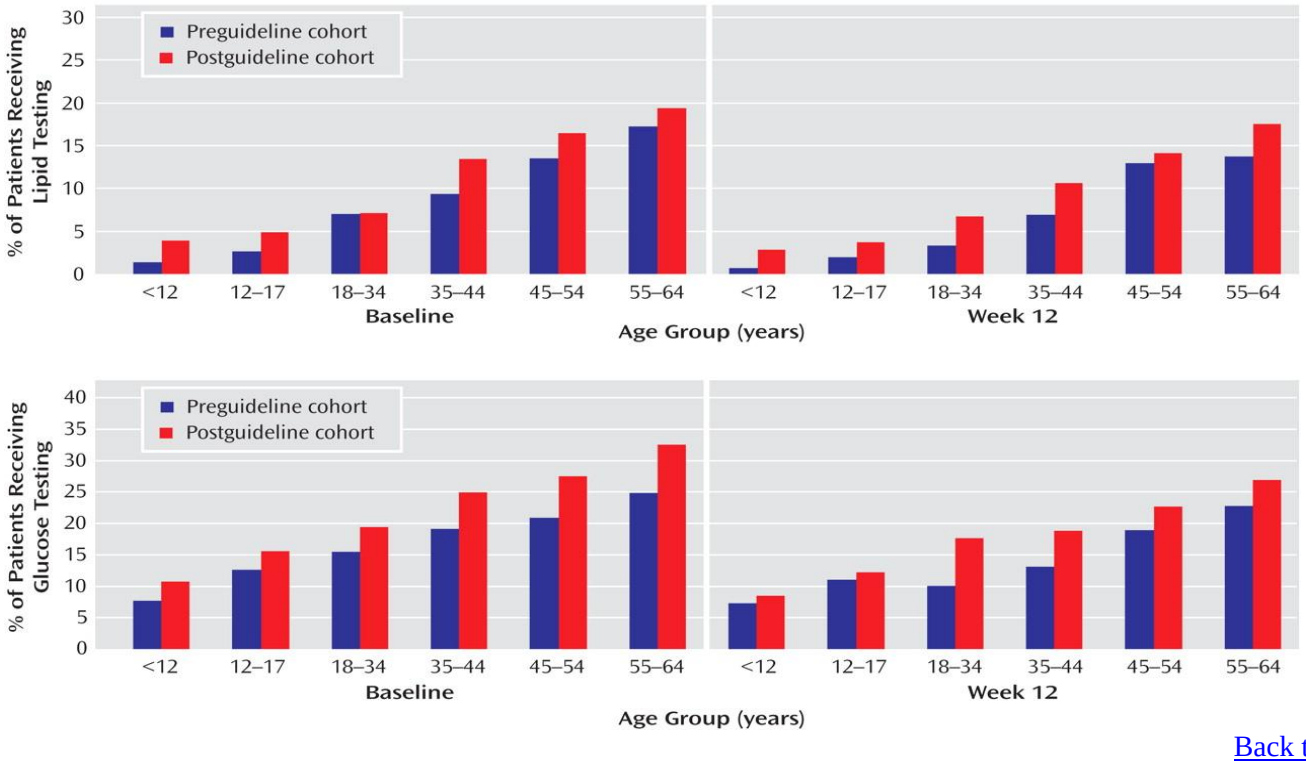
A retrospective analysis of a large managed care database of 23619 patients demonstrates that although the testing of glucose and lipids increased significantly since the publishing of the ADA guidelines in 2004, rates remained inadequate.[1] Table 4 lists the percentages of patients tested before and after the guidelines for lipids and glucose.

TABLE 4

	Lipid Pre	Lipid Post	Glucose Pre	Glucose Post
Baseline	8.4%	10.5%	17.3%	21.8%
12 week	6.8%	9.0%	14.1%	17.9%

Even after the guidelines were published, less than 1 in 4 patients received glucose testing at baseline, and approximately 1 in 10 patients received baseline lipid testing. Testing rates were similar among the 5 drugs tested (aripiprazole, ziprasidone, quetiapine, olanzapine, and risperidone). Rates of testing did increase with age (Figure 3), although this is not surprising since the risk for diabetes, obesity, and hyperlipidemia also increases with age, which leads to more testing in the geriatric population compared to younger patients.

FIGURE 3



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DISCUSSION

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Published guidelines proved to have a minimal impact on the rate of blood glucose and lipid monitoring in patients started on AAs in managed care organizations. Why this is so is not clear.

It is possible that clinicians have not heeded the guidelines due to a lack of evidence regarding the effectiveness testing has on overall health outcomes. There appears to be a positive relationship between adverse effects and efficacy in the AAs, and switching medications to decrease metabolic effects might increase the risk of relapse. Relapse is associated with its own health risks, and is often further complicated the need for in-patient hospitalization, which reduces quality of life and increases morbidity and mortality. Avoiding relapse is usually the most important goal of psychiatrists, and they may be reluctant to change medications on a stabilized patient, which reduces the incentive to test patients.

Another possible explanation is that clinicians still do not grasp the severity of the risks of AAs, suggested by the fact that younger patients are tested far less often than the elderly. Clinicians need to be aware that the AAs metabolic effects do not discriminate based on age, and all patients should be screened according to the ADA guidelines.

CONCLUSION

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Guidelines are only effective when they are followed in clinical practice. To ensure compliance with the guidelines, managed care organizations should set up specific protocols for initial and follow up monitoring of blood values for new patients started on AAs. A quality assurance system should be set up to ensure that the proper tests are ordered in these patients.

Wrong answer…try again or read on.

[Back to quick-read info and quiz question]

Quiz Answer Key:

1. C
2. B
3. A
4. C
5. B

Some Key references:

IHA Provider formulary. www.independenthealth.com. "user: partners, pass: partners"
Individual product information sheets for each drug were also utilized. Links to each provided in first chart.

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