Quetiapine Case 3: Akathisia 1-29-16

Jose de Leon, MD

3. Quetiapine Case 3 (unpublished)

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Think about pharmacological principles in the context of polypharmacy.
2. Appreciate that for understanding quetiapine safety, one must consider:
   - 2.1. Personal, environmental and genetic factors.
   - 2.2. Pharmacodynamics and pharmacokinetics.
3. Be familiar with the concept of akathisia.

Abbreviations

- AED: antiepileptic drugs
- AP: antipsychotic
- C: concentration
- CI: confidence interval
- D: dose
- EPS: extrapyramidal symptoms
- RCT: randomized controlled trials
- Receptors:
  - 5-HT: serotonin
  - β: beta adrenergic receptors
  - D: dopamine
- TDM: therapeutic drug monitoring
- VTA: ventral tegmental area

Terminology Clarification

- *Prescribing information* is the same as:
  - *Package insert* (used in the past)
  - *Drug labeling* (used by PubMed)

Quetiapine Case 3

3.0. Case Description
3.1. Pacing
3.2. Diagnosing Akathisia
3.3. Quetiapine and Akathisia
3.4. Akathisia Pharmacology Review

3.5. Pharmacological Mechanisms in Akathisia

3.6. Pharmacological Mechanism in this Akathisia Case

3.7. Relevance of Akathisia

Quetiapine Case 3

3.0. Case Description
3.1. Pacing
3.2. Diagnosing Akathisia
3.3. Quetiapine and Akathisia
3.4. Akathisia Pharmacology Review
- 3.4.1. Akathisia-inducing Drugs
- 3.4.2. Treatment

3.5. Pharmacological Mechanisms in Akathisia
- 3.5.1. Pharmacokinetic Mechanisms
- 3.5.2. Pharmacodynamic Mechanisms

3.6. Pharmacological Mechanism in this Akathisia Case
- 3.6.1. Pharmacokinetics Mechanisms in this Case
- 3.6.2. Pharmacodynamic Mechanisms in this Case

3.7. Relevance of Akathisia

3.0. Case Description

The patient was followed > 4 years

AP treatment was first quetiapine,

second olanzapine and

third clozapine.

He arrived with 4 AEDs but was switched to only valproate, co-prescribed to APs.

<u>The same patient is used in several presentations:</u>

Quetiapine Case 2: Therapeutic Drug Monitoring

Quetiapine Case 3: Akathisia

Clozapine Case 2: Infection

Valproate Case 3: Formulation

3.0. Case Description

3.0. Quetiapine Case: Description

- 31-year-old Caucasian ♂.
- Smoking under controlled conditions (10 cig/d).
- No access to caffeine beverages.
- Psychosis started at 12 years of age.
- He has been refractory to treatment for many years. He has not lived in the community for the last four years. Moreover, he has been hospitalized in the two most restrictive state forensic units for violent patients. The last facility was a correctional facility.

3.0. Quetiapine Case: Description

- His schizophrenia was characterized by very severe symptoms in the disorganized dimension.
  - His speech & behavior was severely disorganized.
  - His attention span was extraordinarily short, to the point that the patient was unable to answer simple questions relating to time or place orientation.
  - He also exhibited inappropriate affect.
- Other symptoms:
  - He appeared to have paranoid delusions and possibly auditory hallucinations, but it was difficult to assess them due to the agitation and the extraordinarily severe language disorganization.

3.0. Quetiapine Case: Description

- One day after arrival at the treatment-refractory unit, the patient tried to attack a nurse and had to be transferred to a special area of the hospital that has six low-stimuli beds for violent patients.
- This area was designed to be opened as needed and used in order to stabilize patients within a few days; however, this patient was there for 7 months when this happened.

3.1. Pacing

3.1. Quetiapine Case 3: Pacing

- The patient was on quetiapine D =700 mg/day and propranolol D=80 mg/day.
- After phenytoin was discontinued, quetiapine Cs were detected and corresponded to D <75 mg/d (D =700 mg/d).

(See the presentation “Quetiapine Case 2: Therapeutic Drug Monitoring.” It focuses on quetiapine pharmacokinetics).

3.1. Quetiapine Case 3: Pacing

- Then an obvious tremor appeared:
  - Resting and postural.
  - His mother reported that the patient always had tremors with APs.
  - Benztropine did not appear to improve it.
  - After 4 years, Dr. de Leon finally concluded that the tremor was relatively independent of APs.

3.1. Quetiapine Case 3: Pacing

- More worrisome: after an extra 200 mg D of quetiapine (total 900 mg/d):
  - Worsening of tremor
  - Unusual gait (right leg to the side; patient had hip surgery when he was a child)
  - Pacing

3.1. Quetiapine Case 3: Pacing

Why is pacing important?

3.1. Quetiapine Case 3: Pacing

Why is pacing important?

Pacing can be an objective sign of akathisia.

3.1. Quetiapine Case 3: Pacing

What do you do next?

3.1. Quetiapine Case 3: Pacing

What do you do next?

Ask the patient if he feels restless.

3.1. Quetiapine Case 3: Pacing

- Restlessness is a subjective sign of akathisia.
- The patient was too disorganized to answer questions and report restlessness.

3.2. Diagnosing Akathisia

3.2 Quetiapine Case 3: Diagnosing Akathisia

- Dr. de Leon recommends using The Barnes Akathisia Rating Scale:

http://www.ncbi.nlm.nih.gov/pubmed/2574607
http://www.ncbi.nlm.nih.gov/pubmed/14870947

- This scale has scores for
  - Objective Symptoms
  - Subjective Symptoms:
    Awareness of Restlessness
    Distress Related to Restlessness
  - Global Clinical Assessment

3.2 Quetiapine Case 3: Diagnosing Akathisia

- Use observation:
  - while the patient is seated (>2 min)
  - when standing while engaged in neutral conversation (>2 min)
  - in other situations, for example, while engaged in activity on the ward, the patient may also be rated. Subsequently, use direct questioning of subjective phenomena.

3.2. Quetiapine Case 3: Diagnosing Akathisia

- Objective symptoms:
  Characteristic movements are:
  - Shuffling or stamping legs/feet, or
  - Swinging of one leg, while sitting, and/or
  - Rocking from foot to foot or "walking on the spot" when standing (some articles call this "walking in place").

3.2. Quetiapine Case 3: Diagnosing Akathisia

- Severity level of objective symptoms:
  - Mild < 50% time
  - Moderate ≥ 50% time
  - Severe:
    constant restless movements &/or inability to remain seated or standing without walking or pacing

3.2. Quetiapine Case 3: Diagnosing Akathisia

- Subjective symptoms. Awareness:
  - Mild: non-specific restlessness
  - Moderate:
    - aware of inability to keep leg still or
    - a desire to move the legs, and/or
    - complains of inner restlessness

    aggravated when required to stand still
  - Severe: Most of the time:
    - intense compulsion to move and/or
    - strong desire to walk or pace

3.2. Quetiapine Case 3: Diagnosing Akathisia

- Global clinical assessment:

http://www.ncbi.nlm.nih.gov/pubmed/14870947

  - Absent: No awareness of restlessness
    - Pseudoakathisia: No awareness + characteristic movements (A form of tardive dyskinesia or stereotypy associated with psychosis)
  - Questionable: Non-specific inner tension + fidgety movements

3.2. Quetiapine Case 3: Diagnosing Akathisia

- Global clinical assessment (continuation):

□ Mild:	• awareness • fidgety movements (no need of characteristic movements) • little or no distress
□ Moderate:	• awareness • characteristic movements • distressing
□ Marked:	• compulsive desire to walk • remains seated for ≥ 5 min
□ Severe:	• strong compulsion to pace up and down most of time • unable to sit or lie down • intense distress and insomnia

3.1. Quetiapine Case 3: Pacing

- The patient could not answer whether or not he felt restless.
- The nurses knew this patient very well (he stayed for months in this small unit and many days he was the only patient) and were firmly convinced that he was restless. They were very worried because he had very high potential for violence in the absence of akathisia.
- He seemed to have marked akathisia.

3.1. Quetiapine Case 3: Pacing

- These treatment decisions were made:
  - All extra quetiapine Ds for agitation were eliminated.
  - Quetiapine standard D was kept at 700 mg/day.
  - Propranolol D was kept at 80 mg/day.
  - Benztropine 3 mg/day was added, as he appeared to have an abnormal gait and tremor.
- He never had akathisia on quetiapine again.

3.3. Quetiapine and Akathisia

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Is akathisia frequent on quetiapine?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Is akathisia frequent on quetiapine?

No.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you know?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you know?

Look at the prescribing information.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- US prescribing information is available:
  - Go to DailyMed: http://dailymed.nlm.nih.gov/dailymed/about.cfm
  - Type “quetiapine” in the search box:
    > 20 quetiapine fumarate products
    (generic quetiapine is available)
    - Dr. de Leon usually selects original prescribing information (in this case “Astra Zeneca” and not “Extended Release”)

    http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0584dda8-bc3c-48fe-1a90-79608f78e8a0
  - Click on “Adverse Reactions”.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Akathisia in Adults - Percentages

Table[1]	Diagnosis	Duration (weeks)	Quetiapine vs. placebo
9	S or M	3-12	Not described
10	M adjunctive	3	Not described
11	BPD	8	4% vs 1%
12	S	6	[2]0-2% vs 8%

[1]This akathisia table was built using percentages are obtained from these tables described in the prescribing information.
[2]0% in 300 and 600 mg/day and 2% in 75, 150 and 750 mg/day
S: schizophrenia. M: mania. BPD: bipolar depression
http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0584dda8-bc3c-48fe-1a90-79608f78e8a0

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Any other source?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Any other source?

Yes, PubMed.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Go online to PubMed.

http://www.ncbi.nlm.nih.gov/pubmed

- Type “quetiapine and akathisia” in the search box.
- 189 articles appeared (on 1-23-16; later on you may find more). 189 is too many articles to study.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- To reduce the number:
  - Click on “Show Additional Filters”.
  - Select “Search Fields”.
  - Choose “Title”.
- 6 articles appear with the words “quetiapine” and “akathisia” in the title. One is free and relevant:

Shah R, Grover S, Maheshwari U, Kate N, Malhotra N. Acute akathisia with quetiapine: A case report and review of literature. Indian J Pharmacol. 2010 Dec;42(6):416-7. http://www.ncbi.nlm.nih.gov/pubmed/21189919

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Shah et al.:
  - Quetiapine offers a lower incidence of EPS.
  - Accumulated case reports show that quetiapine can lead to akathisia, especially in subjects prone to develop EPS.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Can you look for studies with a higher level of evidence?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Can you look for studies with a higher level of evidence?

Yes.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Go back to the list of 189 articles:

http://www.ncbi.nlm.nih.gov/pubmed

- Look for Meta-Analysis.
  - Click on “more” on “Article Types”.
  - Select “Meta-Analysis”.
  - Click on “Meta-Analysis”.
- There are 11 articles (1-23-16).

One is free and relevant:

Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. Schizophr Bull. 2012 Jan;38(1):167-77. http://www.ncbi.nlm.nih.gov/pubmed/20513652

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Dr. de Leon recommends you download the pdf of Rummel-Kluge et al.'s article and keep it in your computer as an important review on AP EPS.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Rummel-Kluge et al.'s abstract:
  - "Quetiapine showed significantly less use of antiparkinson medication than the 3 other second generation antipsychotics, it was compared with (olanzapine, risperidone, and ziprasidone)."
  - "Scale-derived data (Barnes Akathisia Scale and Simpson Angus Scale) were limited."

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Read the article.
- Go to Figure 3 on the Barnes Akathisia Scale (page 172).
- Very limited data.
- Next slide: statistical reminder.
- The presentation “Introduction to Statistical Concepts Needed for Clinical Pharmacology” explains what CIs are and how to interpret them to get approximated values of significance.

3.3. Quetiapine Case 3: Interpreting Statistics

- Go to Figure 3 (page 172): a meta-analysis comparing APs using the Barnes Akathisia Scale (from baseline to endpoint) http://www.ncbi.nlm.nih.gov/pubmed/20513652
  - The squares on the left half of the page reflect mean differences, MD, described on the right side.
  - Lines emanating from the squares reflect Cis, described on the right side.
  - The main vertical line emerges from 0 (MD=0).
    - squares left of this vertical line: favors studied AP
    - squares right of the vertical line: favors “versus” AP
  - If the lines coming out from squares (reflecting Cis)
    - do not cross vertical line: mean difference $p<0.05$.
    - cross vertical line: mean difference may not be significant.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

- Literature summary by Dr. de Leon:
  - Quetiapine can cause akathisia.
  - Not common; <10% of patients.
  - Patients with akathisia may have particular vulnerability.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Was this patient vulnerable to akathisia?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

Was this patient vulnerable to akathisia?

Yes.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you know?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you know?

You need to know akathisia's pharmacological mechanisms.

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you learn about akathisia's pharmacological mechanisms?

3.3. Quetiapine Case 3: Quetiapine & Akathisia

How do you learn about akathisia's pharmacological mechanisms?

You need to review the pharmacodynamics of offending drugs and akathisia treatments.

3.4. Akathisia Pharmacology Review

3.4. Akathisia Pharmacology Review

3.4.1. Akathisia-Inducing Drugs

3.4.2. Treatment

3.4.1. Akathisia-Inducing Drugs

3.4.1. Quetiapine Case 3: Akathisia Drugs

- D_2 antagonists
  - First- and second-generation APs
  - Anti-emetics: metoclopramide
- SSRIs: most data is from case reports
  - Predisposing factors:
    - multiple akathisia-inducing drugs
    - high D
    - previous akathisia
    - baseline anxiety
    - brain trauma

http://www.ncbi.nlm.nih.gov/pubmed/19289334

3.4.1. Quetiapine Case 3: Akathisia Drugs

- Review of second-generation APs:
  - Less akathisia than first-generation APs
  - RCT frequency: bipolar > schizophrenia

  http://www.ncbi.nlm.nih.gov/pubmed/19389331
- Meta-analysis of second-generation APs:
  - Very limited data on RCTs

  http://www.ncbi.nlm.nih.gov/pubmed/20513652
- Quetiapine offers low risk for akathisia:
  - Probably explained by
    - low affinity for D_2 receptors and
    - loose binding

3.4.2. Akathisia Treatment

3.4.2. Quetiapine Case 3: Akathisia Treatment

- First option: stop AP or ↓ dose.
  Always think about this possibility.
- Consider switching APs.
  - clozapine: virtually absent
  - quetiapine: low risk

- Very few RCTs are available to guide treatment. We are left with the clinician's preference.

3.4.2. Quetiapine Case 3: Treatment

- Dr de Leon's favorite clinical guideline for treating akathisia:

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

  - It lists the treatment drugs described in this presentation.
  - It lists 5 situations and recommends approaches with choices in rank order. Two are described in this presentation.

3.4.2. Quetiapine Case 3: Treatment

- Recommended treatments include:
  - β-blocker: propranolol 10-30 mg (3 times/day)
  - Anticholinergics: benztropine 1-2 mg (2 times/day)
  - Benzodiazepines: lorazepam 1 mg (3 times/day)
    clonazepam 1 mg (2 times/day)
- Other drugs less frequently used:
  - Clonidine: hypotension risk
  - Mirtazapine

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

3.4.2. Quetiapine Case 3: Treatment

- Assuming changes on AP are not possible and no other EPS
  - 1st choice: propranolol 10-30 mg (3 times/day)
  - 2nd choice: benztropine 1-2 mg (2 times/day)
  - 3rd choice: lorazepam 1 mg (3 times/day) or clonazepam 1 mg (2 times/day)

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

3.4.2. Quetiapine Case 3: Treatment

- Assuming that changes of AP are not possible and that other EPS (acute dystonic reaction or parkinsonism) are present:
  - 1st choice: benztropine 1-2 mg (2 times/day)
  - 2nd choice: benztropine + propranolol 10-30 mg (3 times/day)
  - 3rd choice: benztropine + lorazepam 1 mg (3 times/day or clonazepam 1 mg (2 times/day).

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

3.5. Pharmacological Mechanisms of Akathisia

3.5. Pharmacological Mechanisms in Akathisia

3.5.1. Pharmacokinetic Mechanisms

3.5.2. Pharmacodynamic Mechanisms

3.5.1. Pharmacokinetic Mechanisms in Akathisia

3.5.1. Quetiapine Case 3: Akathisia Pharmacokinetics

- Not systematically studied.
- The literature of first-generation APs usually indicates that akathisia may be dose-related since lowering the AP dose is usually recommended.

3.5.2. Pharmacodynamic Mechanisms in Akathisia

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- There are very few studies. You need to use brain imaging or animal models.
- Loonen & Stahl (2011) provided some hypotheses.

http://www.cnsspectrums.com/aspx/articledetail.aspx?articleid=3570

- These are “hypotheses” or “theories” and cannot easily be studied.

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- Extensive (80%) ↓D_2 activity probably causes akathisia.
- Based on this idea, Loonen & Stahl's model proposes: "Akathisia may result from efforts to compensate for dopaminergic underactivity in the nucleus accumbens."

http://www.cnsspectrums.com/aspx/articledetail.aspx?articleid=3570

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- A good akathisia model should explain the therapeutic effects of:
  - β-blockers
  - Antimuscarinic drugs (anticholinergics)
  - GABA (benzodiazepines are GABA-A allosteric modulators)

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- There are no studies comparing akathisia characteristics while on SSRIs and on APs. The literature usually assumes that they are the same type of phenomena.
- If this is true, the pharmacodynamics of SSRI-induced akathisia should be incorporated in akathisia models.

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- Koliscak & Makela summarize prior SSRI akathisia models:
  - Dopamine mesocortical system VTA→prefrontal cortex
  - 5-HT and noradrenaline inhibit dopamine in the VTA. SSRIs: ↑ 5-HT at VTA will ↓ dopamine, causing akathisia.

3.4.2. Quetiapine Case 3: Akathisia Pharmacodynamics

- Loonen & Stahl's article summarizes prior SSRI akathisia models:
  - SSRIs stimulates 5-HT_{2A} → ↓ dopamine release causing akathisia

http://www.cnsspectrums.com/aspx/articledetail.aspx?articleid=3570

3.6. Pharmacological Mechanisms in this Akathisia Case

3.6. Quetiapine Case 3: Akathisia Case

How should you think about the pharmacological mechanism in this akathisia case?

3.6. Quetiapine Case 3: Akathisia Case

How should you think about the pharmacological mechanism in this akathisia case?

First, think about pharmacokinetics.

3.6.1. Pharmacokinetic Mechanisms in This Akathisia Case

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

- Akathisia only occurred when an extra 200 mg dose of quetiapine (total 900 mg/d) was given.
- TDM was obtained. See the "Quetiapine Case 1: Therapeutic Drug Monitoring" if you want more details.

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

Dose mg/day	Peak C ng/ml	C/D ratio
Found		
700 (200/500)[1]		
200 extra	240[2]	0.27[3]
Expected (Company Study)		
225	277[4]	1.2
750 (3 x 250)[5]	778[4]	1.0

[1]Taking 200 mg at early morning and 500 at night
[2]1 hour after 200 mg extra dose
[3]240/900=0.27
[4]1-1.5 hours after last dose
[5]Taking three 250 mg doses

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

- Assuming that TDM data from the company can be compared, this patient had akathisia with a peak of 240 ng/ml, which corresponds to a quetiapine D <225 mg/d (225 mg/day provides a peak of 277 ng/ml).
- Moreover, the patient was taking 80 mg/d of propranolol.

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

- No akathisia with
  - propranolol D: 80 mg/day, and
  - quetiapine D: 700 mg/d.
- Akathisia occurred with
  - propranolol D: 80 mg/day, and
  - quetiapine D: ↑ to 900 mg/d (due to an extra dose of 200 mg).

TDM indicated the “real” quetiapine D was much lower (<225 mg/d).

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

- The patient developed akathisia again:
  - olanzapine D=↑ 5 to 10 mg/day
  - propranolol D= 80 mg/day, and
  - benzotropine D=4 mg/day.

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

What can you conclude about pharmacokinetic mechanisms in this akathisia case?

3.6.1. Quetiapine Case 3: Case Pharmacokinetics

- Akathisia while on quetiapine and olanzapine was dose-related.

- Low serum Cs of quetiapine and low Ds and Cs of olanzapine caused akathisia in this patient.

3.6.2. Pharmacodynamic Mechanisms in This Akathisia Case

3.6.2. Quetiapine Case 3: Case Pharmacodynamics

What can you conclude about pharmacodynamic mechanisms in this akathisia case?

3.6.2. Quetiapine Case 3: Case Pharmacodynamics

- We know very little about akathisia pharmacodynamics.
- This patient was very sensitive to akathisia:
  - Akathisia is not frequent on quetiapine (low affinity for D_2 receptors and loose binding).
  - Akathisia is not frequent on olanzapine.
  - The patient had akathisia with
    - low Cs of these 2 APs that rarely cause akathisia, and
    - akathisia treatments.

3.6.2. Quetiapine Case 3: Case Pharmacodynamics

- The patient never had akathisia on clozapine despite high levels.
- This fact does not say much about this vulnerable patient.
  - Akathisia on clozapine is virtually nonexistent, if it happens at all.
- This fact may support the hypothesis that clozapine probably does not cause akathisia.

3.6.2. Quetiapine Case 3: Case Pharmacodynamics

- There is NO way to prove that clozapine does NOT cause akathisia.
- It is difficult to know if rare clozapine published cases reflect akathisia or not.

3.7. Relevance of Akathisia

3.7. Quetiapine Case 3: Relevance of Akathisia

- Akathisia can contribute to violence.
- Akathisia is possible associated with suicide.

  http://www.ncbi.nlm.nih.gov/pubmed/14870947
- Akathisia is very unpleasant. Kendler:
  - Currently among the top psychiatric researchers
  - During medical school he participated in a study and took 1 mg haloperidol IM. He was impressed by two features:
    - intensity of dysphoria was striking and
    - "dramatic sense of a foreign influence forcing me to move." (Am J Psychiatry 1976;133:454-5)

Thank you

Answers

1. B
2. A
3. C
4. D
5. D
6. D
7. A
8. A
9. A
10. A