

Atypical Antipsychotics in Acute Agitation & Delirium: Are they just along for the RIDE?



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Learning Objectives

- To provide pharmacists with an overview of non-drug measures and pharmacotherapy strategies in managing an acutely agitated patient.
- To review the efficacy evidence and the safety implications of using atypical antipsychotics to treat these patients.
- To review preferred treatment strategies based on the etiology of the agitation.

Delirium

- Acute change (hours to days) in mental status
 - Fluctuations in consciousness and cognitive skills
 - Attention difficulties
 - Memory deficits, disorientation
 - Agitation
 - Apathy, withdrawal, emotional lability
 - Sleep disturbances
 - Perceptual disturbances (hallucinations –visual*)
 - Neurologic signs (unsteady gait, tremor)

Gleason OC, Am Fam Physician 2003;67:1027-34

Characteristics of Delirium

- Three psychomotor variants
 - Hyperactive
 - Hypoactive
 - Mixed
- Prevalence
 - 25 - 30% of hospitalized medical or cancer pts
 - 15-50% of post-op patients
 - 70-87% of ICU patients
 - 60% of nursing home residents

Inouye Sk, NEJM 2006;354:1157-65

Differential Diagnosis of Delirium

- I nfection
- W ithdrawal
- A cute metabolic
- T rauma
- C NS pathology
- H ypoxia
- D eficiencies
- E ndocrine
- A cute vascular
- T oxins or drugs
- H eavy metals



Wise MG, Trzepacz PT. Textbook of consultation-liaison psychiatry, APP 1996

Treatment of Delirium

- Identify & correct the underlying medical condition causing the disorder
- Provide supportive care
 - Hydration, nutrition, mobilizing pt, avoiding restraints, calm environment, assist orientation (clock, glasses, hearing aids), uninterrupted sleep
- Prevent complications
- Treat behavioral symptoms

Acute Agitation

- A state of motor restlessness accompanied by mental tension
- Heightened responsiveness to stimuli
- Irritability
- Inappropriate / purposeless verbal or motor activity
- Decreased sleep
- Fluctuation of symptoms over time

Lindenmayer JP. J Clin Psych 2000;61(suppl 14):5-10
Battaglia J. Drugs 2005;65(9):1207-22

Causes of Agitation



- Psychiatric illnesses
- Drug intoxication or withdrawal states
 - cocaine, amphetamines, alcohol, benzodiazepines, opioids
- Medical conditions
- Medication toxicity

Pathophysiology of Agitation

- Multiple mechanisms involved
 - Depends on the different clinical disorder
- Dysregulation in neurotransmitter systems
 - Increased Dopamine, Norepinephrine
 - Decreased GABA
 - Decreased Serotonin (~increased)

Lindenmayer JP. J Clin Psych 2000;61(suppl 14):5-10

Scales to Measure Severity of Agitation

Measuring Severity of Agitation

- PANSS-EC
 - Positive and Negative Symptom Scale – Excited Component (5 items from total 30)
 - 7-point scale (1 absent – 7 extreme)
 - Poor impulse control
 - Tension
 - Hostility
 - Uncooperativeness
 - Excitement
 - Possible score: 5 – 35
 - ≤ 5 = absent, 6-10 = minimal, 11-15 = mild, 16-20 = moderate, 21-25 = mod-severe, 26-30 = severe, 31-35 = extreme

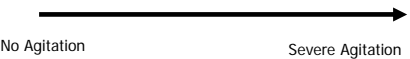
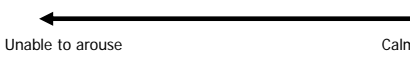
Measuring Severity...

- PANSS-Ag (Agitation Component) score: 5-35
 - Poor impulse control
 - Hallucinatory behavior
 - Hostility
 - Uncooperativeness
 - Excitement
- ABS – Agitated Behavior Scale
 - 14 items, 4-point scale (1 absent, 4 extreme degree)
 - Possible score: 14-56
- BPRS – Brief Psychiatric Rating Scale
 - 24 items, 14 self-report and 10 observational
 - 7-point scale (1 absent – 7 severe)
 - Broad range of symptoms assessed
 - Possible score: 24-168

More Scales...

- OASS – Overt Agitation Severity Scale
 - 12 items, 5-point scale (0 absent, 4 always present)
 - Assesses behaviors = Intensity x Frequency = Severity Score
 - Possible score: 0 – 120
- OAS – Overt Aggression Scale
 - 16 items
 - 4 categories: verbal aggression, physical aggression to self, objects & others
 - Aggression score (max score 21)
 - Total aggression score -accounts for level of restrictive intervention required (max score 26)
- Clinical Global Impression – Improvement Scale
 - 7- point scale
 - very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse

Limitations to Severity Scales

- Assess only one side of the spectrum

- Also need to consider the desirable or undesirable sedation – decreased level of consciousness


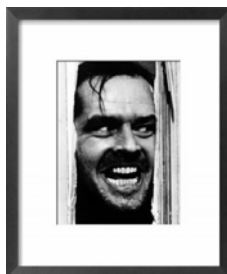
Full Spectrum Scales

- BARS (Behavior Activity Rating Scale) - 7 point scale
 - 1 - unarousable 5 - signs of overt activity but will calm
 - 2 - asleep but responds 6 - extreme/continuous activity but not requiring restraint
 - 3 - drowsy/sedated 7 - violent and requiring restraint
 - 4 - quiet/awake
- ACES (Agitation-Calmness Evaluation Scale) - 9 point scale
 - 1 - marked agitation 6 - moderate
 - 2 - moderate 7 - marked
 - 3 - mild 8 - deep sleep
 - 4 - normal 9 - unarousable
 - 5 - mild calmness
- Provide less detail about the agitation, behaviors
- Gives a sense on whether the patient may be assessed by physicians

Patient Case

Meet Patient JN (also known as JT)

- 45 yr old male
- Brought in to ER by police after altercation at a hotel...
- He is agitated, restless and uncooperative to questions or exam
- He is increasingly hypervigilant with the noises around him in the busy ER
- Denies drug/alcohol use
- No past med history available at this point



Goals of Therapy

- Safe and rapid control of symptoms
- Calming without excessive sedation
- Reduce danger to self and others
- Resumption of therapeutic alliance
- Minimize or avoid side effects

Non-drug Interventions

- Environment
 - Interpersonal communication
 - Physical surroundings
- Non-violent crisis intervention (NVCi)
 - Verbal techniques for de-escalation
 - Physical principles for personal safety techniques
- Show of force
- Restraints
 - Seclusion rooms
 - Physical
 - ... Pharmacological interventions
 - Chemical



Risks with Physical Restraints

- Psychological trauma
- Immobilization – thrombosis, PE
- Rhabdomyolysis
- Catecholamine rush – arrhythmias
- Asphyxia ... death
 - Position, neck compression, reduced forced vital capacity

Back to JN



- More info becomes available
 - Urine tox screen – negative
 - Other labs within normal limits
 - PANSS-EC = 17 (moderate)
 - No known drug allergies or ADR
- A medical resident wanders by and after observing JN – suggests the 'usual remedy' of "5-2-2" (IM Haloperidol, Lorazepam, Benzotropine)

- What are some other options to consider first??
 - Reduce tension and de-escalate crisis
 - Verbal interactions, Empathy
 - Decrease stimulation (seclusion room if necessary)
 - Offer food or beverages
 - Offer voluntary medication

Desirable Characteristics of Medication Choices

- Anti-agitation efficacy
- Rapid onset of action
- Sustained effect
- Low adverse-effect profile
- Permits communication
- Choice of formulation
 - Tablet, rapid-dissolving tablets, liquid, short-acting IM
- Low risk of drug interactions

Pharmacological Treatments of Acute Agitation

- Benzodiazepines (BZD)
- Conventional Antipsychotics (CAP)
- Atypical Antipsychotics (AAP)
- Combination BZD and AP
- Formulation – IM vs. PO
- "Rapid Tranquilization" = calming without sedation

Benzodiazepines

Benzodiazepines

- Pharmacology
 - Enhance GABA effects on chloride channel of GABA-BZD receptor – decreasing cellular excitability
- Lorazepam - drug of choice:
 - Most studied BZD in agitation
 - Predictable IM absorption
 - Intermediate half-life (10-20 hrs)
 - Dose: 1-2 mg SL/PO/IM q30 min
 - Onset: SL 15-30 min, IM 10-20 min
 - Peak effect: SL 60 min, IM 30-60 min
 - Duration: 3-6 hrs

Evidence for BZD

- BZDs at least as effective as Haloperidol (HAL)
- BZD superior than HAL
 - Measures of aggression
 - CGI (Clinical Global Impression)
 - Resolving catatonia
 - More acutely sedating than HAL
- Side effects
 - Excessive sedation, respiratory depression
 - Paradoxical disinhibition

Allen MH. J Clin Psych 2000;61(suppl 14):11-20

Conventional Antipsychotics

Conventional Antipsychotics (CAP)

- Commonly used agents:
 - Haloperidol (HAL) – liquid, tablet, short IM, depot IM
 - Loxapine (LOX) – liquid, tablet, short IM
 - Zuclopenthixol acetate (Clopixol Accuphase®) – special circumstances only
- Pharmacology
 - Dopamine (D2) blockade – “tightly bind”
 - High potency vs. Low potency
 - Histamine (H1) blockade
 - Muscarinic blockade
 - Alpha-1 blockade

CAP - Pharmacokinetics

	Haloperidol	Loxapine	Zuclopenthixol Acetate
Dose	2-10 mg PO/IM q1hprn	12.5-25 mg PO/IM q1hprn Max 50 mg/4hr (not for IV use)	50-150 mg IM prn may repeat dose in ~12-24hr Max 400 mg (avail injection only)
Onset	PO 30 min IM 10-20 min	PO 20-30 min IM 15-30 min	2-4 hrs Sedation may be sooner
Peak effect	PO 3-6 hrs IM 30-45 min	PO 1.5-3 hrs IM ~similar	24-36 hrs
Duration	4-6 hrs	12 hrs	3 days

* High potency * Mid potency * High potency

Evidence for CAP

- Early studies in 1970's showed CAP > Placebo
 - HAL (2.5-5 mg) similar efficacy to LOX (25-50 mg)
 - LOX more effective for sleep
 - LOX peak benefit by 2 hr vs HAL at 6 hr (po)
- Side effects
 - Hypotension, EPS (akathisia, tremor, rigidity, dystonic reactions), Sedation, Anticholinergic effects

Allen MH. J Clin Psych 2000;61(suppl 14):11-20

Haloperidol, Lorazepam or Both?

P	n = 98; RCT, DB Mod – severe psychosis or behavioral dyscontrol Excluded: obvious ETOH intoxic, delirium or CNS depression	
I	Haloperidol (HAL) 5 mg IM	1 st 3 injections at least 1 hr apart, then q2hprn
I	Lorazepam (LRZ) 2 mg IM	
C	Combination HAL 5 mg + LRZ 2 mg IM	
O	Hourly evaluations on BPRS, CGI and ABS for 12 hrs	

Battaglia J et al. Am J Emerg Med 1997;15:335-340.

Results - HAL, LRZ or Both? ...

- All groups - significant improvement from baseline
 - Combination > LRZ on ABS at 1 hr, No diff by 2-3 hrs
 - Combination > LRZ or HAL on mBPRS at 2-3 hrs, No diff by 4 hrs
 - Less drug requirement (3 doses or less of study meds)
 - Combination 91% pts
 - LRZ 74%, HAL 71%
- EPS:
 - HAL 20% (11% dystonic rxn)
 - Combination 6%
 - LRZ 3%

Back to JN



- You opt to try reducing stimulation – quiet room with door open
 - PANSS-EC = 17 (mod)
- He is accepting of oral medications, consider
 - Lorazepam 2 mg PO
 - Loxapine 25 mg + Lorazepam 2 mg PO
 - LOX more sedating than HAL, less well-studied
 - Haloperidol 5 mg + Lorazepam 2 mg PO
- Re-assess in 30-60 minutes
- Check vitals if pt cooperative
- What about an Atypical Antipsychotic??

Atypical Antipsychotics

Atypical Antipsychotics (AAP)

- Available agents in Canada
 - Risperidone – liquid, tablet, rapid-disintegrating tablet, long-acting depot
 - Olanzapine – tablet, rapid-disintegrating tablet, short-acting IM injection
 - Quetiapine – tablet
 - Clozapine – tablet
- Pharmacology
 - Dopamine (D2) blockade – “hit and run” approach
 - Serotonin (5HT-2a) blockade
 - Histamine (H1) blockade
 - Muscarinic blockade
 - Alpha-1 blockade

Action on Receptor	The Good	The Bad
D2 Blockade	Antipsychotic effect	EPS (tremor, rigidity, akinesia, postural instability), Elevated Prolactin, Sexual Dysfunction, Akathisia
5HT-2a Blockade	Antipsychotic effect May decrease EPS Some Anxiolytic, Antidepressant and Antimigraine effects	Hypotension Sedation Sexual Dysfunction
Muscarinic Blockade "anticholinergic"		Dry mouth, blurred vision, Constipation, Drowsiness, Memory problems
Alpha-1 Blockade		Hypotension, Dizziness, Tachycardia, Drowsiness
Histamine Blockade		Sedation, Hypotension, Weight gain

AAP Pharmacokinetics

	Risperidone	Olanzapine	Quetiapine
Dose	1-2 mg q1hprn (daily max 4-6 mg)	5-10 mg q1hprn (max 20 mg/ 4 hr) IM max 30 mg/day	?? Not well established 25-50 mg q6hprn
Tmax	PO: 1.4 hr M-tab®: 1.8 hr Liquid: 1 hr	PO: 4 - 6 hr Zydis®: 4-6 hr IM: 15 - 45 min (IM bioequiv 5x greater than PO)	PO: 1.5 hr
Duration	~ 12 - 24 hr	~ 12 - 24 hr	~ 6 - 12 hr

Currier GW. J of Psychiatric Practice 2006;12:30-40.

Risperidone (RSP) po vs. HAL im (Currier 2001)

P	n = 60, mean age 37 Psychotic agitation Non-randomized, rater-blinded Baseline PANSS-Ag: RSP 28.5, HAL 27 (severe)
I	RSP 2 mg liquid + LRZ 2 mg (PO)
C	HAL 5 mg + LRZ 2 mg (IM)
O	PANSS-Ag and CGI at 30 & 60 min

Currier GW et al. J Clin Psych 2001;62:153-7.

RSP - Currier 2001 - Results

- PANSS-Ag, CGI decreased significantly in both grps at 30 & 60 min
 - No difference between groups
- Limitations
 - non-randomized design (selection bias in pts willing to accept oral meds)
 - single dose AP
- No SE reported in RSP grp, 1 pt in HAL grp – acute dystonia
 - 1 pt in RSP grp required IM HAL for ongoing agitation

RSP po vs. HAL im (Currier 2004)

P	n = 162, RCT, rater-blinded Pts with acute exacerbations of Schizophrenia, Mania, or Delusional disorders. Baseline PANSS-Ag = 19 (moderate), mean age 39 Excluded: delirium, intoxication or withdrawal
I	RSP liquid 2 mg + LRZ 2 mg (PO)
C	HAL 5 mg + LRZ 2 mg (IM)
O	1: Efficacy on PANSS-Ag at 1 hour Repeated measures on PANSS total, CGI, OAS up to 24 hr

Currier GW et al. J Clin Psych 2004;65:386-94

RSP - Currier 2004 - Results

- Efficacy at 1 hr on PANSS-Ag
 - At 1 & 2 hrs – both groups improved (PANSS-Ag 13)
 - 1/3 pts used ~2.5 mg LRZ at 20 hrs both grps
- Adverse Effects
 - movement disorders: 8 pts IM, 4 pts PO
 - orthostatic hypotension 2 pts IM
- Limitations
 - single dose AP
 - comparing IM to PO

RSP po vs. HAL po (Veser 2006)

P	n = 30, pilot study, RCT Agitated or psychotic pts. (allowed substance abuse) Mean age 40 Baseline PANSS total: RSP 88, HAL 90, PBO/LRZ 65
I	RSP 2 mg PO + LRZ 2 mg IM
I	HAL 5 mg PO + LRZ 2 mg IM
C	Placebo PO + LRZ 2 mg IM
O	BPRS and total PANSS at 30 & 90 min

Veser FH et al. J of Psych Practice 2006;12:103-8

RSP - Veser 2006 - Results

- Outcomes PANSS, BPRS at 30 & 90 min
 - No SS differences between grps
 - PANSS total reductions: RSP -31, HAL -24, PBO/LRZ -11
 - BPRS total reductions: RSP -22, HAL -22, PBO/LRZ -12
 - Trend for great improvement in RSP/LRZ and HAL/LRZ arms
- Limitations
 - lacked power
 - short follow-up of 90 min (missed peak effects of AP)
- No SE reported

Veser FH et al. J of Psych Practice 2006;12:103-8

Olanzapine (OLZ) – RIDE Study (Baker 2003)

- Randomized, 4 day DB, 3 day OL trial (n = 148)
 - Acutely agitated with Schizophrenia/affective, Bipolar mania
 - Baseline PANSS-EC = 23 (moderate)
 - Excluded substance-induced psychosis

RIDE: Rapid Initial Dose Escalation
 OLZ 20 mg/d + prn OLZ 10 mg
 (Max OLZ 40 mg/d on Days 1-2,
 Max 30 mg/d on Days 3-4)

UCP: Usual Clinical Practice
 OLZ 10 mg/d + prn LRZ 2 mg
 (Max LRZ 4 mg/d on days 1-2,
 Max 2 mg/d on days 3-4)

Open label OLZ 5-20 mg/d (Day 5-7)

Baker RW et al. J Clin Psychopharmacology 2003;23:342-348

OLZ – RIDE Trial Results

- Medication Requirements at 24 hr
 - RIDE: OLZ 29 mg, LZM 0.12 mg
 - UCP: OLZ 10 mg, LZM 2.15 mg

Number of doses at 24 hr:

Group	0 doses	1 dose	2 doses
RIDE	43%	25%	32%
UCP	32%	34%	34%

OLZ – RIDE Results...

- 1° Endpoint: PANSS-EC change at 24 hrs
 - RIDE: -7.01
 - UCP: -5.51 (p=0.003)
 - Absolute difference of 1.5 points / 35 total -- ?? Clinical Significance
 - Both groups (ss) improved from baseline
- 2° Endpoints

24 hrs	CGI-I: RIDE = UCP OASS: RIDE = UCP
48 hrs	PANSS-EC: RIDE = UCP CGI-I: RIDE = UCP OASS: RIDE > UCP (by 0.6 pts/ 120 total)
72 hrs	CGI-I: RIDE > UCP (by 0.6 pts/ 7 total) OASS: RIDE > UCP (by 5 pts/ 120 total)

OLZ – RIDE ...

- Adverse events
 - No significant differences between tx grps for abnormal movements or akathisia
- Excluded substance abuse, pts > 55yrs
- No ECG monitoring done, no vital signs reported

	RIDE	UCP
Somnolence	31%	26%
Headache	17%	8%
Dizziness	15%	7%
Insomnia	13%	8%
Nervousness	7%	11%
Wt gain at 1 wk	1.45 kg	1.21 kg

OLZ po vs. HAL po (Kinon 2004)

P	N = 100, 3 week, Randomized, DB Acutely agitated in-pts with Schizophrenia, Schizoaffective d/o Mean age = 39, Baseline mPANSS = 38 (max 60)	
I	OLZ 10 mg PO + LRZ 1-2 mg po/im prn	Could increase AP dose by 5 mg/day (range 10-20 mg)
C	HAL 10 mg PO + LRZ 1-2 mg po/im prn	
O	mPANSS at 24 hr	

Kinon BJ et al. Am J Emerg Med 2004;22:181-186

OLZ - Kinon 2004 - Results

- Primary outcome mPANSS at 24 hr
 - 24 hrs: Both grps improved from baseline
 - No difference between grps
 - -10 improvement on mPANSS
 - 21 days: OLZ superior to HAL
 - mPANSS -14 vs. -11; p=0.044
- Mean dose at 21 days
 - OLZ 17.1 mg, HAL 15.7 mg
- Only 57 pts completed 3 wk study
 - Discontinued due to SE: OLZ 1.9%, HAL 16.7%

Kinon BJ et al. Am J Emerg Med 2004;22:181-186

OLZ - Kinon 2004 – Adverse Effects

	OLZ	HAL
Dystonia	0%	8.3%
Hypertonia	0%	8.3%
↑ salivation	0%	8.3%
Headache	11.5%	25%
Nervousness	7.7%	16.7%
Anxiety	11.5%	4.2%
Somnolence	17.3%	25%
Wt gain	2.8 kg	-0.64 kg

Quetiapine (QTP) – (Currier 2006)

P	Open-label pilot study, n = 20 Pts exhibiting psychosis or mod-severe agitation. Mean age = 39, Baseline PANSS-EC = 17-18 (moderate) Excluded: obvious drug/alcohol intox, concurrent tx with CYP 3A4 inducers/inhibitors
I	100, 150, or 200 mg QTP - MD perception of clinical need 2 nd dose of QTP or LRZ permitted at 90 min (dose not specified)
O	1 ^o : PANSS-EC at 120 min. (Success = 40% reduction from baseline). 2 ^o outcome: BARS Safety: SBP & pulse at baseline, 30, 60, 90, 120 and 180 min (Orthostasis defined as 20 pt change)

Currier GW et al. J of Psychiatric Practice 2006;12:223-228.

QTP - Currier 2006 - Results

- Median dose 2 mg/kg
 - 7 x 100 mg, 6 x 150 mg, 7 x 200 mg
- PANSS-EC reduction
 - ½ pts had a 40% reduction in scores (success)
 - BARS - reduction from 5 to 3
- Safety
 - 40% pts had orthostatic hypotension by 2 hrs
- Limitations
 - Very small pilot study
 - Agitated pts often present in volume depleted state and are at high risk for medication-induced hemodynamic instability

JN ...



- More information from family
 - JN has a history of Schizoaffective disorder
 - non-compliant with treatment due to lack of insight
 - Treated with Risperidone 3 mg/day in the past
- JN is exhibited psychotic symptoms – appears to be responding to auditory hallucinations
- His behavior is escalating – PANSS-EC = 23 (moderate-severe)

- Consider AAP
 - RSP studied in broader agitated population (psychosis NOS)
 - OLZ studied only in Schizophrenia, Bipolar agitated pts
 - Limited data with QTP
 - Reasonable alternatives if able to take PO
 - both have rapid disintegrating tablets (not studied)
- If agitation worsens, consider IM injections
 - HAL 5 mg + LRZ 2 mg, or LOX 25 mg + LRZ 2 mg
 - Re-assess in 30 minutes
- What about Olanzapine IM?

OLZ IM in Schizophrenia

P	2 trials, n = 555 total, RCT, DB, 24 hrs Mean age 36-38 yrs, Baseline PANSS-EC = 19 (moderate)	
I	OLZ 2.5 – 10 mg IM (dose finding) OLZ 10 mg IM	Max 3 injections, 2 hr apart
I	HAL 7.5 mg IM	
C	PBO IM	
O	PANSS-EC at 2 hrs	
R	OLZ IM similar to HAL IM, both superior to PBO OLZ 2.5 mg arm not as effective as other doses.	

Brier A et al. Arch Gen Psych 2002;59:441-8. Wright P et al. Am J Psych 2001;158:1149-51.

OLZ IM in Bipolar Mania

P	n = 201, RCT, DB, 24 hrs Mean age = 40, Baseline PANSS-EC = 13 (mild)	
I	OLZ 10 mg IM	Max 3 doses in 3 hrs. 3 rd dose: OLZ 5 mg, LRZ 1 mg, PBO group were given OLZ 10 mg
I	LRZ 2 mg IM	
C	PBO	
O	PANSS-EC at 2 hrs	
R	OLZ IM superior to LRZ IM and PBO LRZ similar to PBO at 2 hrs	

Meehan K et al. J Clin Psychopharmacol 2001;21:389-97.

OLZ IM in Dementia

P	n = 272, RCT, DB, 24 hrs (* not indicated for dementia in Canada) Mean age = 78, Baseline PANSS-EC = 19.7 (moderate)	
I	OLZ IM 2.5, 5 mg	Max 3 doses in 3 hrs. 3 rd inj: ½ dose, PBO grp received OLZ 5 mg IM
I	LRZ IM 1 mg	
C	PBO	
O	PANSS-EC at 2 hrs	
R	OLZ IM 2.5, 5 mg and LRZ IM superior to PBO No difference between OLZ IM or LRZ IM	

Meehan K et al. Neuropsychopharmacol 2002;26:494-504.

OLZ IM – Safety information

- ECG monitoring done at baseline, 2 hrs, 24 hrs
 - Clinically significant QTc prolongation
 - OLZ 4-10%, HAL 14%, PBO 19%
 - ? Missed the peak effects of OLZ IM
- Schizophrenia trials
 - OLZ – Hypotension 4%, Parkinsonism 3%, Akathisia 5%
 - HAL – Parkinsonism 17%, Akathisia 8%, Acute dystonia 5%
- Bipolar trial
 - OLZ – one case of syncope
 - No difference for EPS, no acute dystonic rxns (vs. LRZ)

OLZ IM – Safety Information...

- Safety notification letter from manufacturer in Sept/04
 - SAEs reported with co-administration of OLZ IM with other drugs
 - im/po – Haloperidol, Lorazepam, Midazolam, Chlorpromazine
 - Combination can induce hypotension, bradycardia, respiratory/CNS depression
- Recommended
 - NOT to co-administer with parenteral BZDs (** within 1 hr)
 - NOT for use in pts whom substance use is suspected

OLZ IM Study Limitations

- Not compared against standard clinical practice (HAL 5 mg + LRZ 2 mg IM)
 - Comparative HAL dose too high – impact on SE
 - Not compared to LOX (more sedating, less dystonia than HAL)
- Studied in mild-moderate agitation with defined psychiatric diagnoses without serious medical co-morbidities
- No data on use in Substance abuse
- Cost implications ~ \$20/10 mg dose
 - \$2-5 for IM LOX or HAL
 - \$1-6 for rapid-dissolving RSP or OLZ
 - pennies for PO LOX or HAL

Patient Case

Meet SL...

- 39 yr old male
- Brought to ER from an after-party of Banff Seminar
- He has been dancing all night but has become increasingly agitated & restless
- Friends report he had only 2 drinks – they wonder if something was slipped in his drink?
- No past med hx
- T 39 C, BP 195/110

Suspected Substance Induced Agitation

- BZDs are treatment of choice
- Would NOT use monotherapy APs, avoid if possible
 - Deleterious effects on BP
 - Potential for QTc prolongation, arrhythmias
 - Additional anticholinergic effects (hallucinogens)
 - Potential for serotonin syndrome (amphetamines)
 - Potential for EPS, Neuroleptic malignant syndrome
- BZDs offer seizure protection

Remember Drug Interactions

- Olanzapine
 - Metabolized by CYP 1A2
 - 1A2 is strongly induced by cigarette smoking
 - 1A2 is inhibited by ciprofloxacin, fluvoxamine, fluoxetine
 - May need higher doses in heavy smokers
- Risperidone
 - Metabolized by CYP 2D6
 - 2D6 is inhibited by paroxetine, fluoxetine
 - 2D6 is induced by carbamazepine
- Haloperidol
 - Metabolized by CYP 3A4, 2D6
 - Induced by carbamazepine, rifampin
 - Inhibited by phenytoin
- Quetiapine
 - Metabolized by CYP 3A4, 2D6
 - As above

Summary of Drug Interventions

- Offer PO if patient cooperative
 - PO CAP studied in broader pt populations (+ BZD)
 - PO AAP studied mainly in psychiatric populations
 - Consider long-term treatment plan, rapid-dissolve tabs
 - Would NOT recommend RIDE strategy for OLZ
- IM evidence
 - Mainly with HAL, although LOX used in clinical practice
 - OLZ evidence limited to mild-mod agitated psych populations
 - NOT combined with BZDs



Summary...

- Substance-induced agitation suspected
 - BZD 1st choice
 - Monotherapy AP not recommended
 - These pts usually excluded from the trials
 - No data with IM OLZ
- Re-assess for efficacy and toxicity!!!
 - 30-60 min post PO dose
 - 15-30 min post IM dose

Thank-you !!
Any questions??

