Is Quetiapine Just Keeping Them Quiet?

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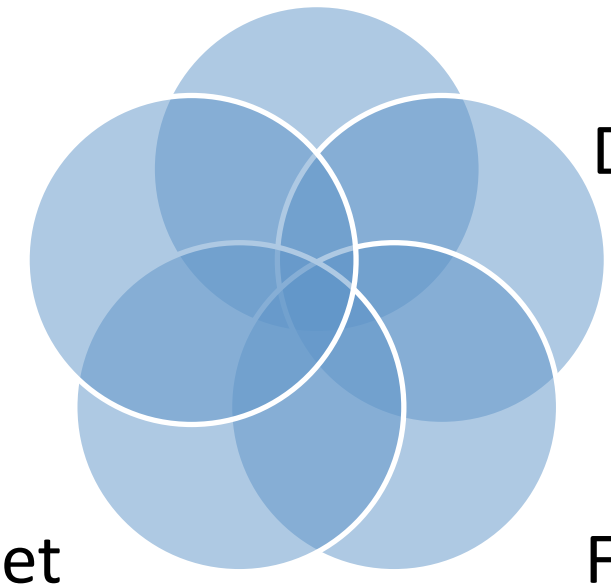
Consultation Liaison Psychiatry

- 76 yo female admitted to general medicine 2 days ago with pneumonia
- Not oriented to time or place
- Acute onset, disturbing auditory hallucinations
- Flat affect alternating with agitation and crying spells
- Query new onset dementia or depression?

Delirium: Diagnostic Features

Inattention

Cognition



Disorientation

Acute onset

Fluctuating

DSM-V

Clinical variants

- **Hyperactive** level of psychomotor activity, mood lability, agitation, and/or refusal to cooperate with medical care

- **Hypoactive** psychomotor activity, sluggishness and lethargy that approaches stupor

- **Mixed** normal level of psychomotor activity. Attention and awareness are disturbed. Or rapidly fluctuating activity level

Epidemiology

Admission to medical unit

- 10 to 20% on admission
- 5-10% during admission

Long term care 6 to 14%

Surgical 10 to 15%

Cardiac surgery 30%

Hip fracture 50%

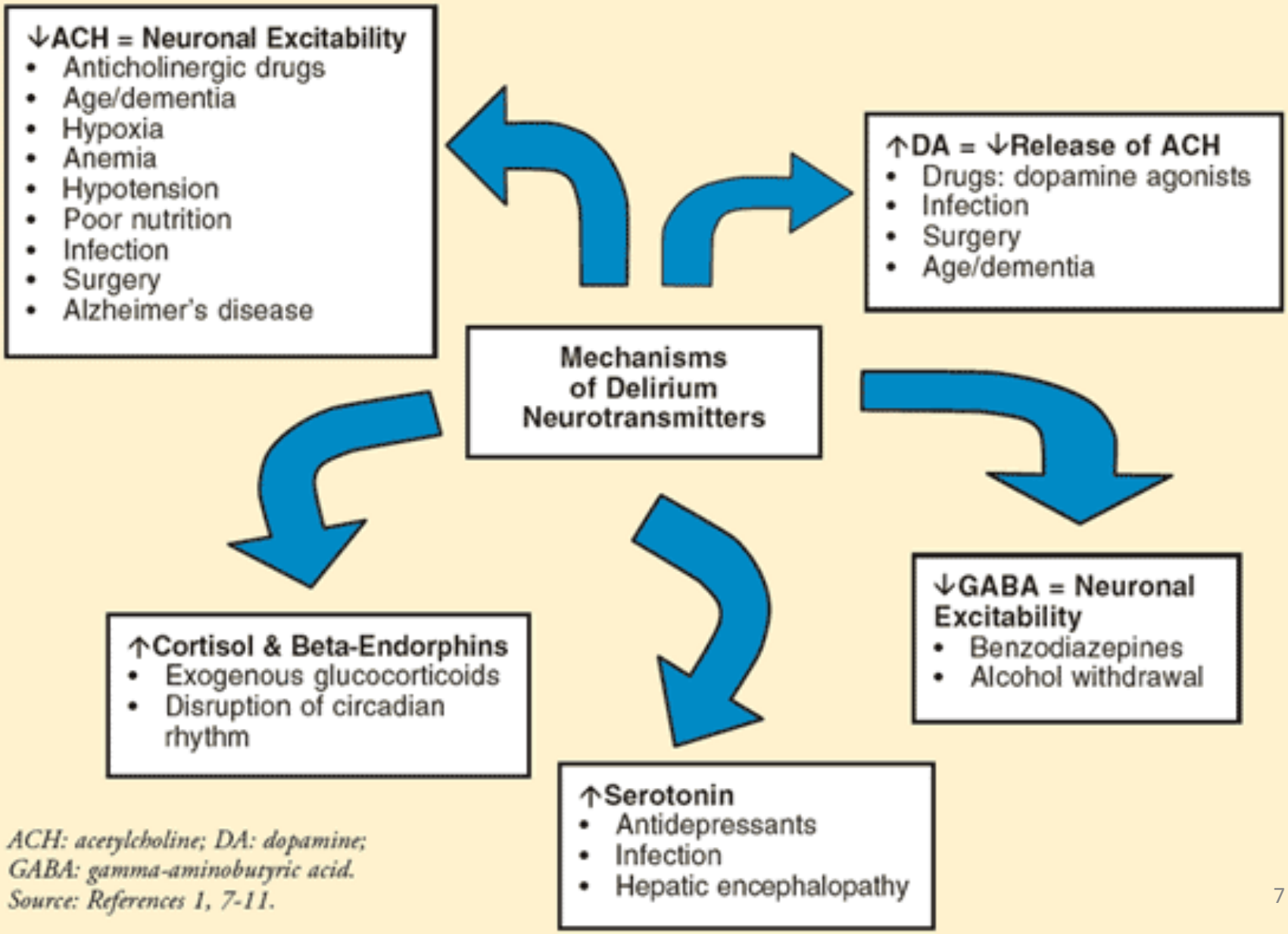
ICU age >65 70%

Palliative advanced cancer 80%

Outcomes

- Independently associated with
  - Mortality
    - I month 16%
    - 6 months 26%
  - Length of hospital stay
  - Increased functional disability
- Symptoms often persist to 6 months

Figure 1. Factors Contributing to Changes in Neurotransmitters, Leading to Delirium



ACH: acetylcholine; DA: dopamine; GABA: gamma-aminobutyric acid.
Source: References 1, 7-11.

Guideline recommendations

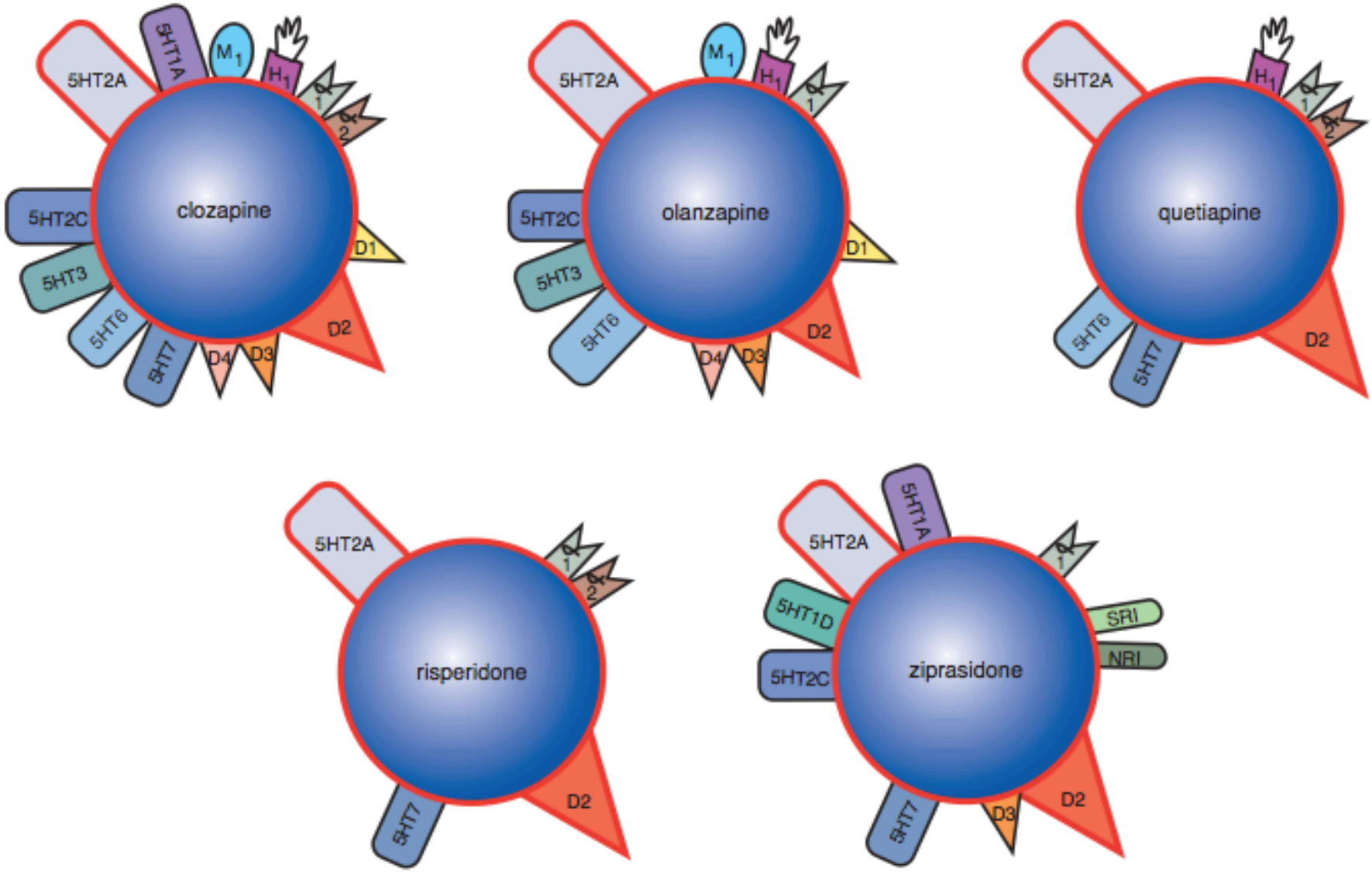
- 2013 American College of Critical Care Medicine
  - There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence)
  - Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C)

- 2006 National Guideline for Seniors Mental Health
  - Haloperidol is suggested as the antipsychotic of choice based on the best available evidence to date. [B]

- 2004 American Psychiatric Association guidelines on delirium
  - Haloperidol as the antipsychotic of choice
    - tranquilizing effect
    - lack of active metabolites
    - limited anticholinergic
    - sedating side effects

Journal of Hospital Medicine 2013;8:215–220
The Canadian Journal of Geriatrics: 2006 (9)S2
Crit Care Med 2013; 41:263–306

Figure 3. Receptor Binding Profiles of the Atypical Antipsychotics[a]



[a]Reprinted with permission from Stahl.[11]
Abbreviations: α_1 = α_1-adrenergic, α_2 = α_2-adrenergic, D = dopamine, 5HT = serotonin, H = histamine, M = muscarinic, NRI = norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor.

Ki the inhibition constant

A measure of the binding affinity of a ligand (e.g., antidepressant) for its receptor

- <1 very potent
- 1-10 potent
- 10-100 some clinical effect
- >100 may not be clinically relevant
- >1000 negligible
  - depends on concentration used for therapeutic effect

N-Desalkylquetiapine vs Quetiapine

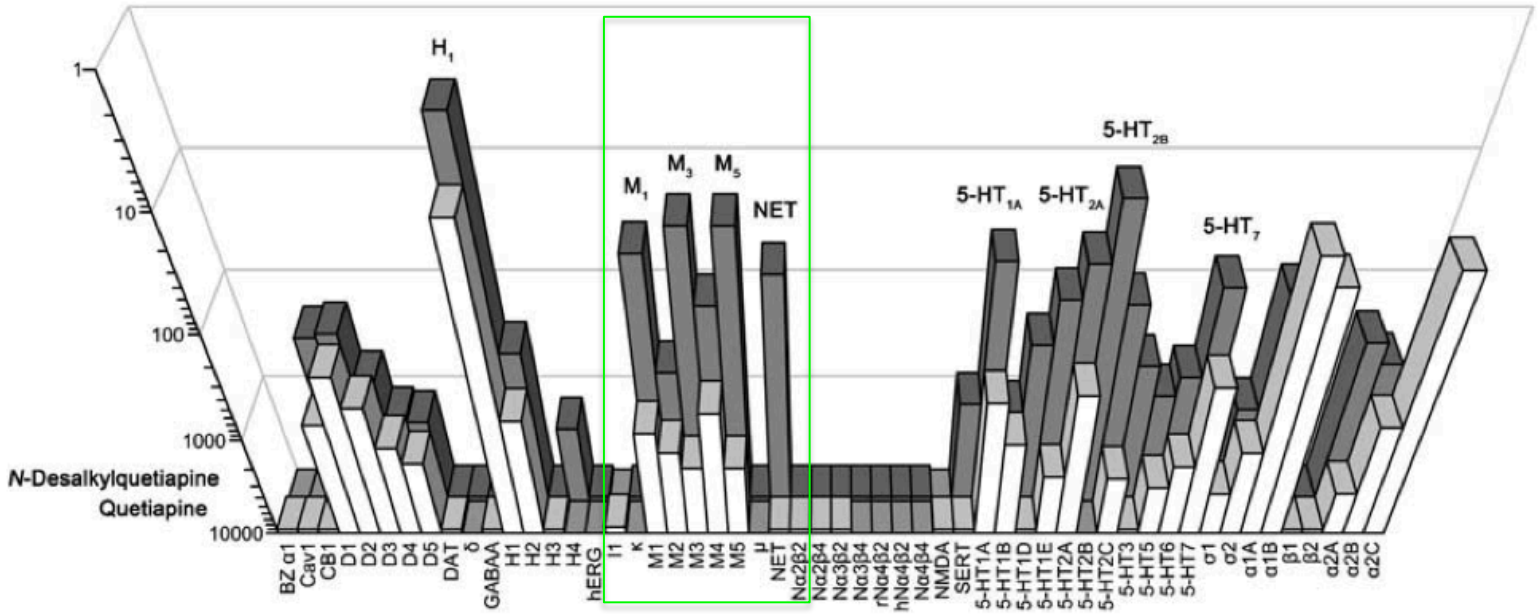


Figure 2 Binding affinities of quetiapine (white bars) and its metabolite *N*-Desalkylquetiapine (dark bars) at the tested panel of brain receptors, ion channels, and neurotransmitter transporters (K_i in nM on a logarithmic scale; no bar, not tested).

Neuropsychopharmacology 2008: 33;2303–12

P	Hospitalized patient with delirium
I	Quetiapine
C	Placebo Alternative antipsychotics Haloperidol
O	Mortality Ventilator time Length of stay Time to baseline cognition Safety

Search

Databases	Medline, Cochrane, Clinical trials.gov, Google Scholar, IPA, Web of Science, EMBASE
Search terms	Quetiapine, neuroleptic, antipsychotic, delirium
Limits	Clinical trial, humans, English
Results	**RCT:** 2010 Tahir quetiapine vs placebo 2010 Devlin quetiapine vs placebo 2013 Maneeton quetiapine vs haloperidol **Randomized prospective:** 2005 amisulpride vs quetiapine **Prospective observational:** 2003 Kim n=12 2004 Pae n=22 2003 Sasaki n=12 2007 Maneeton n=22 **Retrospective:** 2000 Schwartz n=11 2011 Wan n=17 **Systematic Reviews (antipsychotics for delirium):** 2006 Ann Pharmacotherapy 2007 Pharmacotherapy 2007 Cochrane 2009 Psychiatry & Clinical Neurosciences 2011 J Am Geriatr Soc 2013 Journal of Hospital Medicine

shm Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

REVIEWS

Quetiapine for the Treatment of Delirium

Stefanie B. Hawkins, PharmD[1], Mason Bucklin, PharmD[2], Andrew J. Muzyk, PharmD[3]*

[1]Emergency Medicine, University of Kansas Hospital, Kansas City, Kansas; [2]Department of Pharmacy, University of Rochester Medical Center, Rochester, New York; [3]Department of Pharmacy Practice, Campbell University School of Pharmacy and Health Sciences, Buies Creek, North Carolina, and Department of Psychiatry and Behavioral Sciences, Duke University, Durham, North Carolina.

"The trials summarized suggest that quetiapine resolves symptoms of delirium more quickly than placebo and has equal efficacy compared to haloperidol and the atypical antipsychotic amisulpride."

Journal of Hospital Medicine 2013;8:215–220.

Journal of Psychosomatic Research 69 (2010) 485–490

A randomized controlled trial of quetiapine versus placebo in the treatment of delirium☆

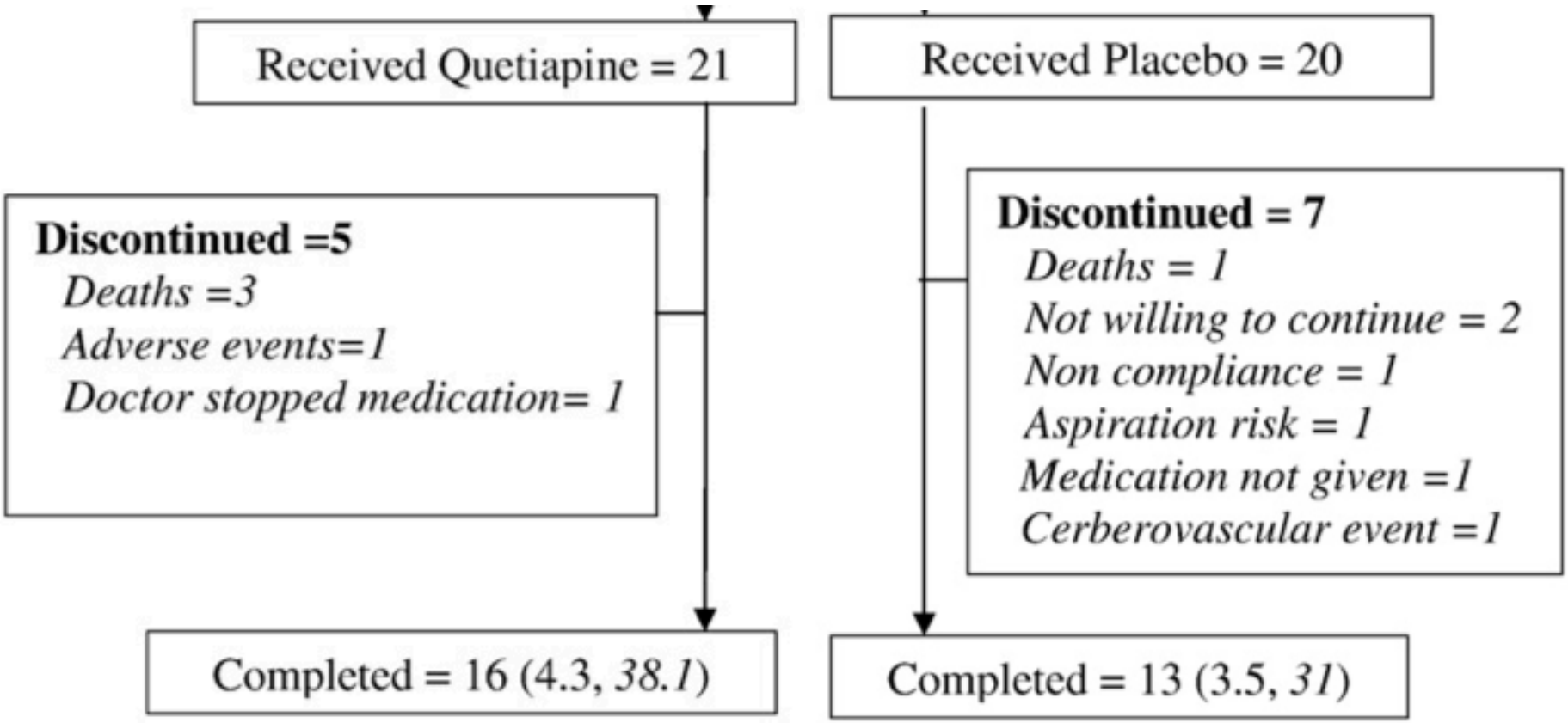
Tayyeb A. Tahir[a,*], Eamonn Eeles[b], Venugopal Karapareddy[c], Prem Muthuvelu[d], Sian Chapple[e], Bethan Phillips[f], Toyin Adyemo[g], Daniel Farewell[h], Jonathan I. Bisson[i]

Tahir TA et al, 2010

DB, single center, RCT, N=42

P	DSM-IV criteria for delirium Delirium Rating Scale Revised 98 (DRS-R-98) total score of > 15 -Medical, surgical and orthopedic patients from June 2003 to April 2005 -70% female -Mean age 84
I	Quetiapine 25 mg once daily orally ↑ by 25 mg/day to max 175 mg/day
C	Matching placebo
O	1 ° mean difference in DRS-R-98 Safety: Abnormal Involuntary Movements Scale (AIMS)

115 patients identified with delirium → 42 recruited



Rate of abnormal involuntary movements

- ✧in 10 days quetiapine 4.8%; placebo 14.3%

Results: total DRS-R-98

	Quetiapine (SE) n=21	**Placebo (SE) n=21**
Baseline	22.7	22.7
Day 3	11.98 (3.11)	14.3 (2.64)
Day 10	8.2 (4.2)	8.5 (4.133)
% <15 at day 7	18 (85.7%)	17 (80.9%)

Tahir TA et al, 2010

- Author's conclusions
  - "Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium."
- AstraZeneca UK sponsored
  - Negative primary outcome, conclusions did not mention, stated an alternative outcome not pre-specified
- Did not meet calculated sample size
  - Sixteen patients from the quetiapine group and 13 from the placebo group completed the study
- Excluded a large number of patients
  - 115 patients were identified as having delirium and 42 recruited

Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study*

John W. Devlin, PharmD; Russel J. Roberts, PharmD; Jeffrey J. Fong, PharmD; Yoanna Skrobik, MD; Richard R. Riker, MD; Nicholas S. Hill, MD; Tracey Robbins, RN; Erik Garpestad, MD

Crit Care Med 2010 Vol. 38, No. 2

Devlin JW et al, 2010

≥4 for inclusion and ≤3 for 1° outcome

DB, multi center, RCT, N=36

P	ICU patients with delirium Intensive care delirium screening checklist ≥ 4 (ICDSC) Order for prn haloperidol IV 75% medical ICU 63 yo
I	Quetiapine 50 mg every 12 hours Titrated based on prn haloperidol usage (max 200 mg every 12 hr)
C	Placebo *Patients in both groups permitted **haloperidol IV 1 to 10 mg q2h prn**
O	1° Time to first resolution of delirium –ICDSC ≤3 first detected 2° total hours in delirium Total hours spent "deeply sedated" (SAS ≤2) or "agitated" (SAS ≥5) Total haloperidol dose in received in mg

Devlin JW et al, 2010

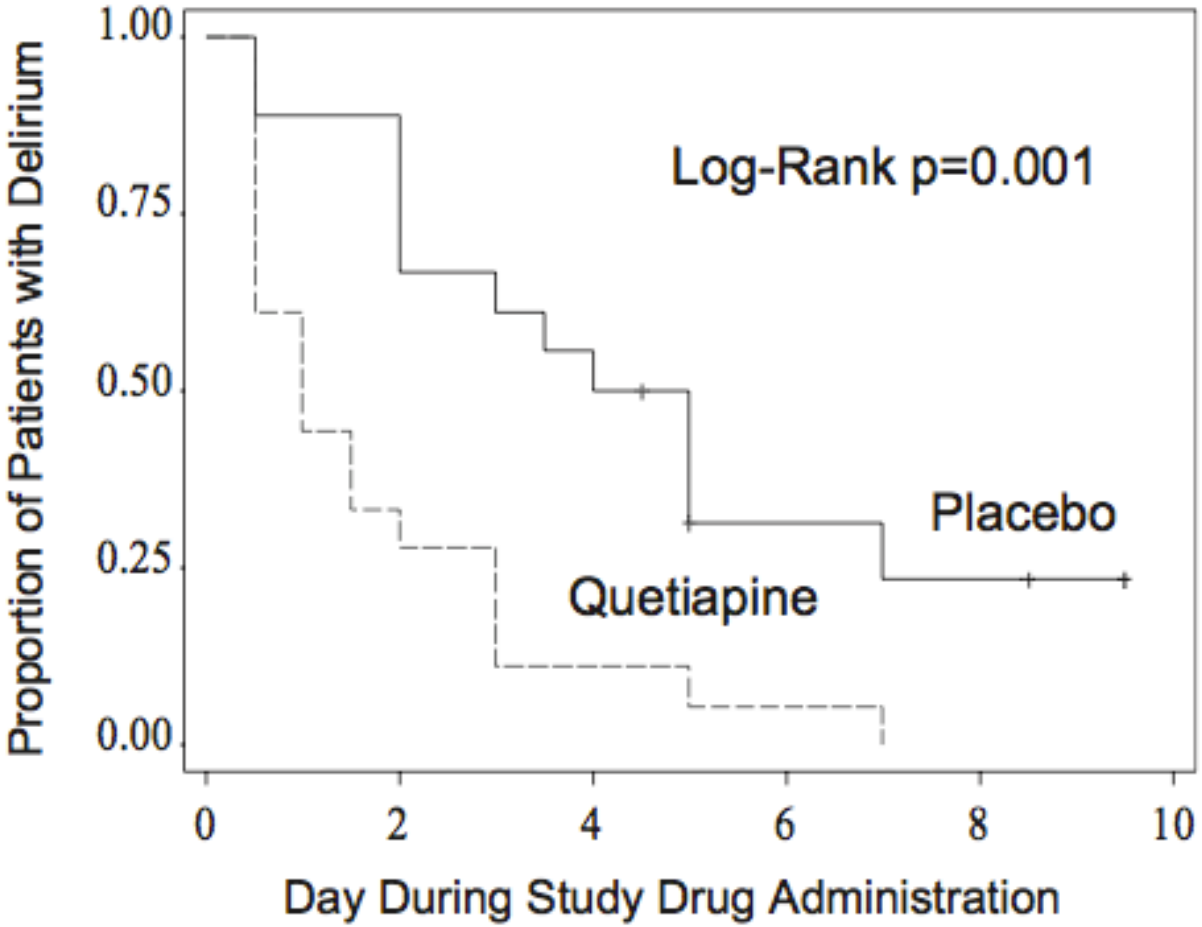
Table 1. Study exclusion criteria

History of irreversible cognitive dysfunction (e.g., dementia) based on a review of the patient record
Admitted with a primary neurologic condition or injury (e.g., intracranial hemorrhage, active seizure)
History of hepatic encephalopathy or end-stage liver disease (Childs-Pugh class B or worse)
Actively withdrawing from alcohol
Treatment with an antipsychotic agent in the 30 days before ICU admission
Current treatment with dexmedetomidine or a neuromuscular blocker
Current treatment with an agent having either the potential to affect quetiapine concentrations (e.g., phenytoin) or increase the risk for QTc prolongation (e.g., erythromycin or any class Ia, Ic, or III antiarrhythmic)
Baseline QTc interval ≥500 msec
Pregnancy
Non-English speaking
Presence of a condition preventing delirium assessment (e.g., coma, severe hearing disability)
Prognosis considered hopeless
Informed consent could not be obtained from the legally authorized representative

ICU, intensive care unit.

258 screened→222 excluded

Devlin JW et al, 2010



median [IQR]: 1.0 [0.5–3.0] vs. 4.5 days [2.0 –7.0]; p = .001

Devlin JW et al, 2010

	Quetiapine	Placebo	P
Time spent agitated, Sedation-Agitation Scale ≥5			
Hours	6 (0–38)	36 (11–66)	.02
%	3 (0–22)	21 (8–41)	.03

Table 4. Other clinical outcomes[a,b]

	Quetiapine (n = 18)	Placebo (n = 18)	*p*
Duration of mechanical ventilation, days	11 (3–19)	11 (4–29)	.67
Duration of intensive care unit stay, days	16 (10–22)	16 (13–32)	.28
Duration of hospitalization, days	24 (11–33)	26 (17–49)	.32
Hospital mortality, %[c]	11	17	1.0

Median (interquartile range)

Devlin JW et al, 2010

	Quetiapine	**Placebo**	**P**
Haloperidol Amount per day (mg)	1.9 (0.8–3.8)	4.3 (1.2–6.1)	.26
Amount of midazolam equivalents per day (mg)	5.3 (0–42)	26.5 (0.3–74)	.32
Fentanyl Amount per day (mcg)	0 (0–65)	170 (14–1089)	.02

Median (interquartile range)

Table 6. Safety outcomes during study drug administration[a]

	Quetiapine (n = 18)	Placebo (n = 18)	p
Adverse events[b]	54	69	.29
Study drug-related adverse events[c]	6	2	.39
Subjects who experienced a study drug-related adverse event, %[d]	28	11	.4
Episodes of somnolence	5	2	.56
Subjects experiencing somnolence, %[d]	22	11	.66
Episodes of hypotension	1	0	.79
Subjects experiencing hypotension, %[d]	6	0	1.0
Episodes of EPS	0	0	1.0
Serious study drug-related adverse events[e]	0	0	1.0
Episodes of QTc interval >60 msec above baseline	20	34	.7
Subjects experiencing QTc interval >60 msec above baseline, %[f]	39	44	1.0
Episodes of QTc interval prolongation[g]	30	41	.32
Subjects experiencing QTc prolongation, %[f,g]	50	72	.31
Episodes of QTc interval >500 msec	8	8	1.0
Subjects experiencing QTc interval >500 msec, %[d,f]	22	28	1.0

Devlin JW et al, 2010

- Authors conclusions
  - "Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation."
- Did not meet sample size
  - 24 subjects in each group would provide 80% power to find a significant difference
- Lacks generalizability
- >20 outcomes analyzed
- More somnolence noted in the quetiapine
  - Not statistically different but are we just sedating these patients
- Only one assessment method used for inclusion
- No standard definition for the resolution of delirium

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
23 July 2013

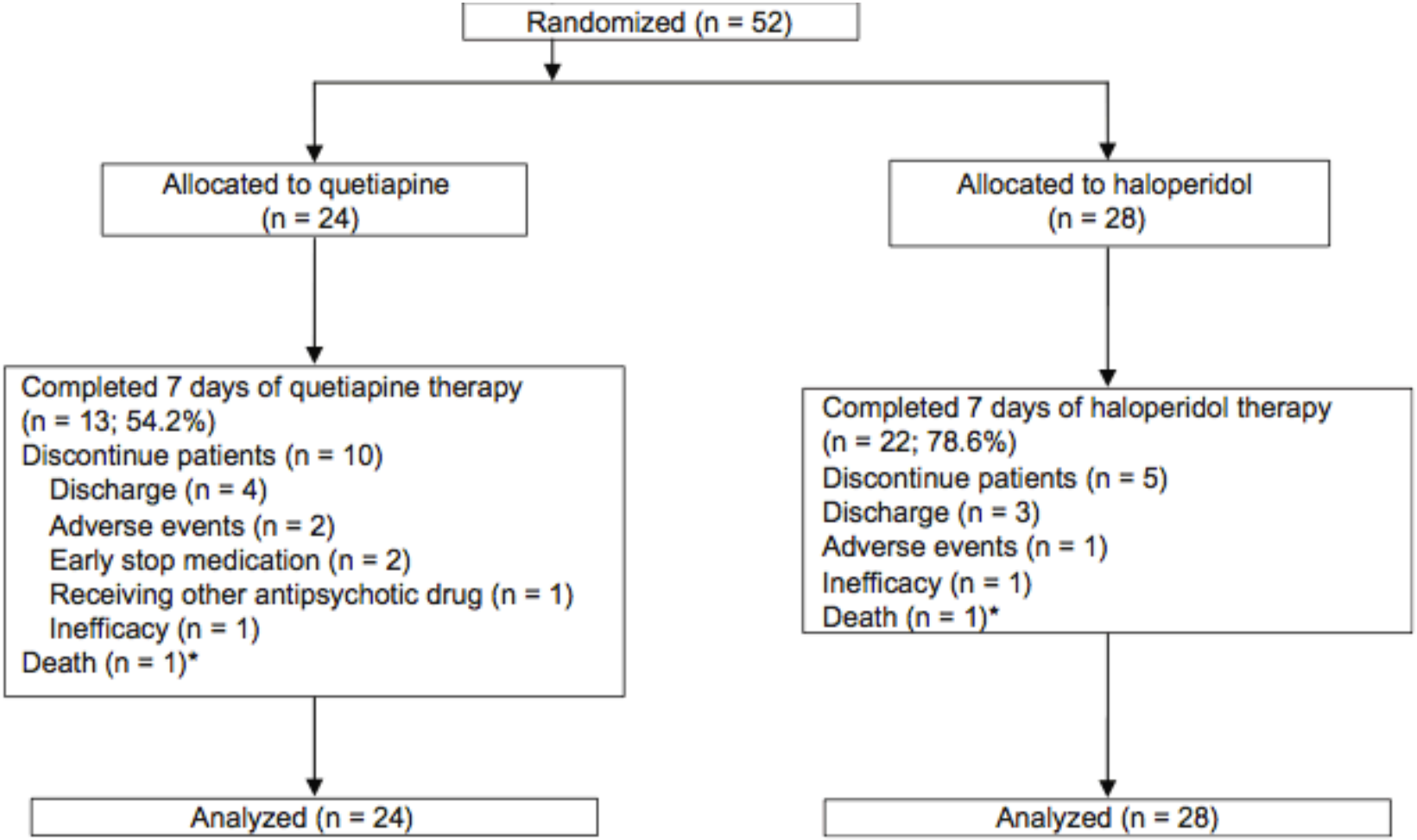
Drug Design, Development and Therapy 2013:7 657–667

Maneeton B et al, 2013

DB, Single center, RCT, N=52

P	DSM-IV criteria for delirium CAM Baseline DRS-R-98 of 29.4 Included patients with dementia -In-patients, tertiary care hospital, Thailand 2009-2011 -Mean age 57 -67% male
I	Quetiapine 25–100 mg/day (mean 67.6 (9.7) mg/day)
C	Haloperidol 0.5–2.0 mg/day (mean 0.8 (0.3) mg/day)
O	1° mean difference in DRS-R-98 at 7 days Response: ≥ 50% reduction in DRS- R-98 severity score from baseline Remission: DRS-R-98 severity score < 12 without relapse Total time of sleep Safety: Modified Simpson-Angus Scale

408 patients screened 52 patients recruited



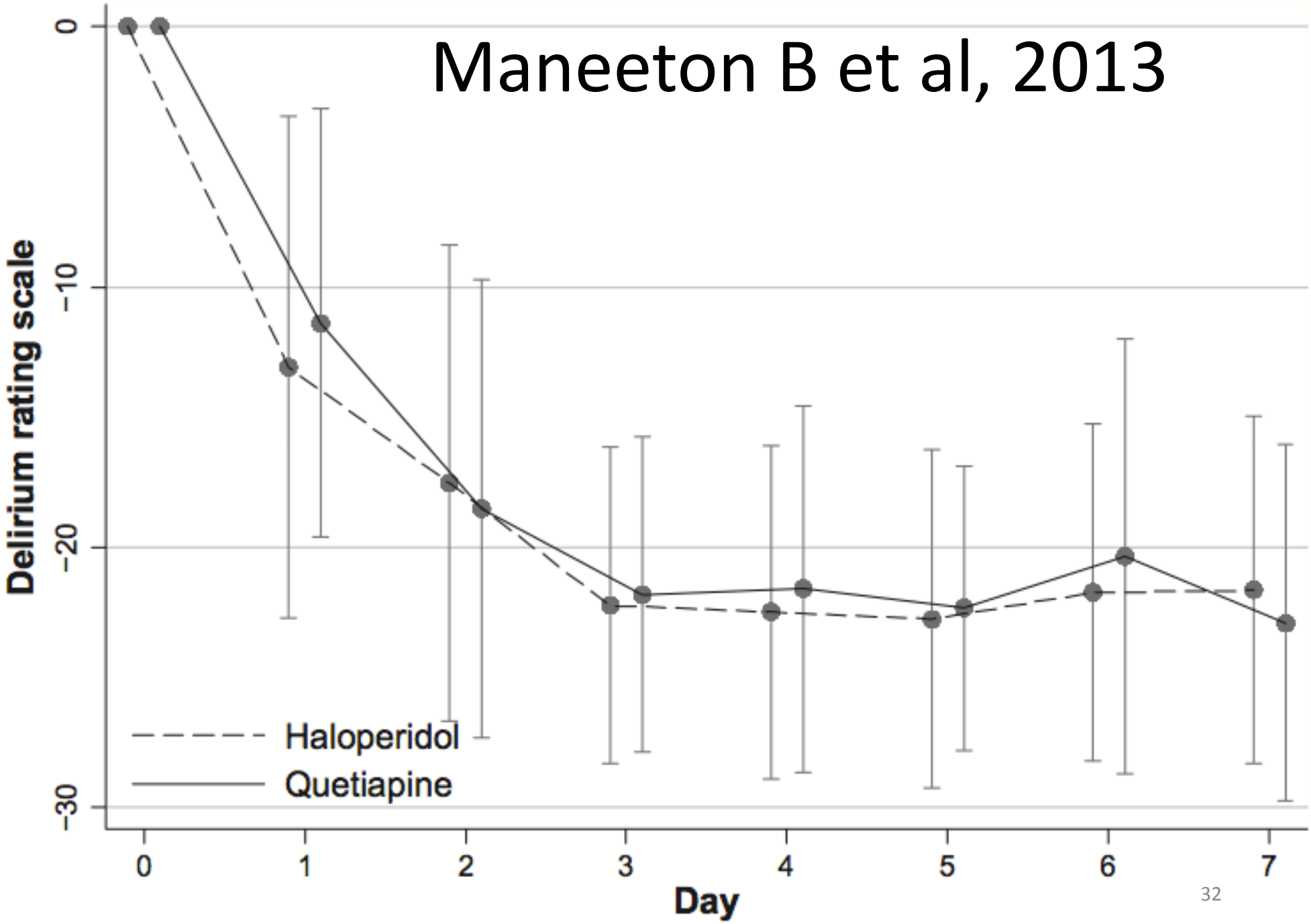
- 13 quetiapine and 22 haloperidol treated patients completed the study

Maneeton B et al, 2013

Table 2 Mean difference of scoring between day 7 and baseline

	Quetiapine Mean ± SD (95% CI)	**Haloperidol Mean ± SD (95% CI)**	***P*-value**
Delirium rating scale-revised-98 scores	−22.9 ± 6.9 (−26.9 to −19.0)	−21.7 ± 6.7 (−24.7 to −18.6)	0.59
Noncognitive subscore	−16.9 ± 5.5 (−20.1 to −13.7)	−15.8 ± 4.7 (−18.0 to −13.7)	0.54
Cognitive subscore	−6.0 ± 3.2 (−7.9 to −4.1)	−5.8 ± 3.6 (−7.5 to −4.2)	0.89
Clinical global impression, improvement	−1.1 ± 1.0 (−1.7 to −0.6)	−1.2 ± 1.4 (−1.8 to −0.5)	0.96
Sleep time (hours)	6.5 ± 3.0 (4.8 to 8.2)	6.1 ± 3.4 (4.6 to 7.7)	0.74

Maneeton B et al, 2013



Maneeton B et al, 2013

Response: reduction in DRS-R-98 severity score from baseline for 50% or more

- Quetiapine 79.2% vs haloperidol 78.6% (*P* 0.97)

Remission: DRS-R-98 severity score < 12 without relapse

- Quetiapine 75.0% vs haloperidol 67.9% (*P* 0.96)

Table 3 Summary of adverse events seen in the study sample

Side effects	Quetiapine group number (%)	Haloperidol group number (%)	*P*-value
Hypersomnia	10 (41.7)	8 (28.6)	0.32
Tremor	0 (0)	1 (3.6)	1.00
Nightmare	1 (4.2)	0 (0)	0.46
Rash	1 (4.2)	1 (3.6)	1.00
Akathisia	0 (0)	1 (3.6)	1.00
Tics	0 (0)	1 (3.6)	1.00
MSAS scores	0.3 (0.7)	0.3 (1.1)	0.51

Two patients died

- one in each group

Maneeton B et al, 2013

- Authors Conclusions:
  - "Low doses of both quetiapine and haloperidol are equally effective and safe for the management of behavioral disturbance in delirious patients"
- Did not meet sample size calculation
- Patients with disorders of cognition included however number in each group not noted
- Comparable doses?
- Increase in sleep time
- Author's discussion point:
  - "While an even bigger sample would perhaps shed more light on potential differences of pharmacological effects, this study appeared to achieve high power meaningful results in a group which is difficult to study"

Summary

			Efficacy	Safety
Tahir	Quetiapine	Placebo	No difference shown in difference in delirium severity	?
Devlin	Quetiapine	Placebo + prn haloperidol	Faster time to first resolution of delirium	?
Maneeton	Quetiapine	Haloperidol	Not powered to detect difference	?

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Drug Safety and Availability

- Postmarket Drug Safety Information for Patients and Providers
- Drug Safety Information for Healthcare Professionals
- Public Health Advisories (Drugs)

Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances

The issues described in this communication have been addressed in product labeling (see Drugs@FDA).

4/11/2005

The Food and Drug Administration has determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Of a total of seventeen placebo controlled trials performed with **olanzapine** (Zyprexa), **aripiprazole** (Abilify), **risperidone** (Risperdal), or **quetiapine** (Seroquel) in elderly demented patients with behavioral disorders, fifteen showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients. These studies enrolled a total of 5106 patients, and several analyses have demonstrated an approximately 1.6-1.7 fold increase in mortality in these studies. Examination of the specific causes of these deaths revealed that most were either due to heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia).

www.fda.gov/Drugs/DrugSafety

Conclusion

- Positive trials with major methodological flaws
- Little confidence in results
- Larger trials appropriately powered vs placebo
  - psychiatrist confirmed presence and resolution of delirium
- Limit use to patients that are at risk of harm to self and others because of delirium symptoms

Q&A

Extras…

Prospective observational

Kim 2003 N=12*	DRS	18.25 ± 6.05	8 ± 2.34 at 5.91 days	25 mg bid titrated to stabilization X1 month
Sasaki 2003 n=12	DRS-J	18.1 ± 4.2	all patients <12 by day 7	25 or 50 mg titrated based on clinical judgment
Pae 2004 N=22**	DRS-R-98	21.8 ±3.2	9.3 ± 3.8 at 8.5 days	Flexible dose
Maneeton 2007 N=17	DRS	24.5 ± 3.2	88.2% >50% at 7 days	25 mg to 100 mg daily

J Med Assoc Thai 2007;90:2158-63
J Clin Psychiatry 2003;64:1316–21
J Geriatr Psychiatry Neurol 2003; 16:29–31
Hum Psychopharmacol Clin Exp 2004; 19: 125–127

Safety in Open Label Trials

Trial	Mortality	EPS	QT/Cardiac	Nightmares	Sedation
Pae					5
Maneeton		2	↓ BP 2	3	13
Kim	1 MI			1	2
Sasaki					

The use of psychotropic medications to treat the symptoms of delirium should be reserved:

a) for patients in significant distress due to agitation or psychotic symptoms;
b) in order to carry out essential investigations or treatment; and/or
c) to prevent older delirious persons from endangering themselves or others

Canadian Coalition for Seniors' Mental Health
The Canadian Journal of Geriatrics: 2006 (9)S2

- 2006 Ann Pharmacotherapy
  - studies evaluated here suggest that antipsychotic drugs are efficacious, when compared with baseline, and safe for the treatment of delirium. Haloperidol remains the most studied agent. Recommendation of one antipsychotic over another as a first-line pharmacologic intervention in the treatment of hospital-associated delirium is limited

- 2007 Pharmacotherapy
  - Atypical antipsychotics vs haloperidol
  - These studies demonstrated that atypical antipsychotics are as efficacious as haloperidol
  - Lower EPS

- 2007 Cochrane
  - These studies compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. Decrease in delirium scores were not significantly different comparing the effect of low dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (Odds ratio 0.63 (95% CI 10.29 to 1.38; P = 0.25)

- 2009 Psychiatry & Clinical Neurosciences
  - Atypical antipsychotics appear to be effective and safe in symptomatic treatment of delirium but the evidence is limited and inconclusive. There are no double-blind, placebo-controlled studies assessing the efficacy and safety of these agents in delirium. Further research is needed with well-designed studies.

- 2011 J Am Geriatr Soc
  - Because of severe methodological limita- tions, the studies in this review do not support the use of anti- psychotics in the treatment of delirium in older hospitalized adults. Additional well-designed randomized placebo- controlled trials are needed.

Critical Care 2011: 5:R215

Table 2 Proportion of patients experiencing resolution and time to first resolution for the delirium symptoms[A]

Delirium symptoms derived from ICDSC	Resolved during therapy[A] N (%)			Time to first resolution[A] (hours; median (IQR))		
	Quetiapine (n = 14)	Placebo (n = 15)	[B]P-value	Quetiapine (n = 14)	Placebo (n = 15)	[C]P-value
Agitation	5 (100.0)	6 (100.0)	-	84 (48 to 204)	36 (24 to 60)	0.07
Decreased level of consciousness	5 (83.3)	6 (100.0)	0.30	36 (24 to 72)	24 (12 to 96)	0.78
Inattention	12 (92.3)	11 (73.3)	0.19	84 (24 to 168)	180 (72 to 240)	0.12
Disorientation	11 (85.6)	8 (72.7)	0.47	48 (12 to 216)	204 (36 to 240)	0.10
Hallucinations/delusions	2 (100.0)	1 (100.0)	-	48 (24 to 72)	156 (144 to 156)	0.22
Hyperactivity	5 (100.0)	6 (100.0)	-	120(60 to 192)	24 (12 to 48)	0.04
Hypoactivity	7 (77.8)	6 (66.7)	0.60	72 (48 to 132)	168 (96 to ne)	0.17
Inappropriate speech or mood	6 (85.7)	3 (100.0)	0.49	132(60 to 192)	72 (24 to 168)	0.31
Sleep/wake cycle disturbance	5 (62.5)	6 (60.0)	0.91	192 (24 to ne)	228 (144 to 240)	0.36
Symptom fluctuation	11 (100.0)	7 (53.8)	0.009	4 (1 to 10)	14 (7 to ne)	0.004

Tools

	Description	Goal	Cut off
DRS	10 items max score 32	Assess severity	12
DRS-R98	16 items 3 items aid in diagnosing max score 39	Assess severity	15
ICDSC	8 item	Screening	4

Cost

- **quetiapine (quetiapine fumarate) 25mg TEVA-QUETIAPINE**
  - Oral tablet
  - BC Pharmacare: FULL benefit for Groups B,C,F,MH,U
  - Unit Price: 0.13 Packaging: 30/100/500

http://www.medi-mouse.com/drugfind.php

Cost

- **haloperidol 1mg APO HALOPERIDOL TAB 1MG**
- Oral tablet
- BUTYROPHENONES
- BC Pharmacare: FULL benefit for Groups B,C,F,MH,PC,U
- Unit Price: 0.20 Packaging: 100/1000

http://www.medi-mouse.com/drugfind.php

Exposure to active metabolite

	Quetiapine	Norquetiapine
Cmax (ng/mL)	660.3	144.1
AUC (ng h/mL)	2,469	1,154.7

*@ steady state following quetiapine 200 mg daily
J Child Adolesc Psychopharmacol 2008;18(1):81-98

PDSP Home | Ki DB Home | Tracer Database | GPCR Database | Roth Lab | U N C | Binding Assay | Functional Assay | MDR-1 / CaCo2 | Publications | UCSD-Nature | NIMH

PDSP
K Database

The database has 55524K_i values for searching, and is growing

This list shows the top 100 Receptors/Targets in K_i

Please let us know if you feel we should add any papers or data. We welcome all feedback/suggestions/comments

Other features on K_i DB are: Download K_i, Data Mining, CDD Interface allows mining K_i database by structure, substructure or structure similarity. Anatomical profiling of GPCR expression is offered for selected targets.

Make a new search

No results matched your search criteria. However, K_i DB supports two types of wildcards.
% represents zero or many characters and _ (underscore) represents one character.

Example 1: Enter 5%ht% in the receptor textbox, Ki DB will retrieve all values for the serotonin subtypes.
Example 2: Enter 5-ht2_ in the receptor textbox, Since _ represents just one character, Ki DB will retrieve all values for the 5-HT2A, 5-HT52B and 5-HT2C.

You can use these wildcards in any of the textboxes. Receptor, Species, Source, Hot Ligand, Test Ligand, and Reference.

Ki ID: [ ] Retreive This Result Only

Receptor: Not Specified / NULL
Receptor: [ ]

Species: Not Specified / NULL
Species: [ ]

Source: Not Specified / NULL
Source: [ ]

Hot Ligand: Not Specified / NULL
Hot Ligand: [ ]

Test Ligand: Not Specified / NULL
Test Ligand: quetiapine

Reference: Not Specified / NULL
Reference: [ ]

Ki is greater than: [ ]
Ki is less than: [ ]
All Ki values

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