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CATIE-AD [1,2]

The Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease (AD)

National Institute of Mental Health (NIMH) **C**linical **A**ntipsychotic **T**rials of **I**ntervention **E**ffectiveness-**A**lzheimer's **D**isease

TRIAL BACKGROUND [3,4,5,6]

- > 90% of pts with dementia develop at least 1 behavioural or psychiatric symptoms. Non-drug approaches to management are recommended; however, antipsychotic drugs are also used despite uncertainty about overall efficacy and safety

TRIAL DESIGN: Double-blind, placebo-controlled, multicentre 42 U.S. sites trial; ITT analysis

- **Assessed the use of antipsychotics in outpatients w/ AD** excluding Lewy Body/Vascular and agitation, aggression, or psychosis
- Compared: olanzapine[OLZ], quetiapine[QUE], and risperidone[RIS] to placebo[PL] → physicians determined starting doses on clinical judgment & patient response
  - Superiority design for each atypical vs placebo; non-inferiority +/- superiority design between agents

POPULATION: 421 patients treated for up to 36 weeks

- **~77 years**, **MMSE 15±~6**, ADAS-cog total score ~35; NPI: **delusions 82%,** hallucinations 49%, **agitation or aggression 86%,** depression 61%; on cholinesterase inhibitor 60%; received antipsychotic ≤2 wks prior 14%
- 73% reside at home, 10% assisted-living; **57% equivalent to assisted-living facilities care**; 17% equivalent to nursing home care

Table I. Results: Primary endpoint: time to discontinuation of treatment for any reason

HR (95% CI)	Olanzapine n=99	Quetiapine n=94	Risperidone n=84	Placebo (PL) n=139	Comments
Initial Dose mg/day Mean{range}	**3.2** {0-10}	**34.1** {0-100}	**0.7** {0.5-2.5}	-	There were no differences between any agent and PL in primary endpoint for time to DC for any reason. ("Time to DC" based on 50th percentile)
Last Dose mg/day Mean {range}	**5.5** {0-17.5}	**56.5** {0-200}	**1** {0-2}	-	
Time to DC: Any Reason HR vs PL (CI) {% of pts}	8.1 wks (5.1-11.6) 0.83 (0.62-1.11); {80%}	5.3 wks (3.6-8.1) 1.01 (0.75-1.36); {82%}	7.4 wks (5.0-12.0) 0.88 (0.64-1.20); {77%}	8.0 wks (5.0-9.3) 1 {85%}	
Time to DC: For Efficacy HR (CI) vs PL	22.1 wks (12.1-?) **0.51** (0.35-0.74)	9.1 wks (7.0-21.6) 0.81 **NS** (0.57-1.15)	26.7 wks (6.4-11.6) **0.61** **(0.41-0.89)**	9.0 wks (6.4-11.6) 1	Efficacy favored OLZ & RIS.* - OLZ & RIS non-inferior to each other HR 0.84 (0.53-1.32) - OLZ superior to QUE HR 0.63 (0.41-0.96)
D/C for AE, intolerability, or death. HR vs PL (CI)	**4.32** **(1.84-10.12)**	**3.58** **(1.44-8.91)**	**3.62** **(1.45-9.04)**	1	Tolerability favored PL. - QUE, RIS superior to OLZ (2° analysis)
	25% D/C rate	16% D/C rate	18% D/C rate	5%	Overall DC: 63% @ 12 wks

* Note: Greater efficacy w/ OLZ & RIS; offset by ↑ AEs, especially for OLZ (see Table II) CI=confidence interval HR=hazard ratio

Table II. *Significant* Adverse Event, Safety Outcomes

No. (%) [NNH vs. PL]	Olanzapine (n=100)	Quetiapine (n=94)	Risperidone (n=85)	Placebo (PL) (n=142)
Any Serious AE	14 (14)	17 (18)	9 (11)	19 (13)
Sedation	**24 (24)** NNH=6	**21 (22)** NNH=6	13 (15)	7 (5)
Parkinsonism or EPS	**12 (12)** NNH=9	2 (2)	**10 (12)** NNH=10	1 (1)
Confusion / mental status Δ	**18 (18)** NNH=8	6 (6)	**9 (11)** NNH=18	7 (5)
Weight ↑>7% - # (%) **{Weight change lb/mo of tx}**	**10/90 (11)** **{1.0 ± 0.4}**	5/80 (6) {0.4 ± 0.6}	**8/75 (11)** **{0.7 ± 0.4}**	4/128 (3) {-0.9 ± 0.3}

◆Safety data limited by short duration of treatment. ◆ limited long-term role; ~80% DC tx by 36wks. ◆NB: MMSE scores did not worsen in CATIE-AD; Ballard et al. demonstrated clinically significant cognitive decline SIB change >10 pts with QUE vs. PL during longer follow-up period 6 & 26 wk

BOTTOM LINE:

- There were no significant differences between any atypical antipsychotics and placebo for overall rate of discontinuation.
- Atypical antipsychotics offer limited efficacy in the long term management of BPSD; non-drug therapies should be considered.
- Any benefit of atypical antipsychotics is largely offset by their adverse events. Therapy should be individualized & reassessed periodically. As 80% stopped therapy by 36 weeks, consider routine reassessment in 3-6months for both efficacy & tolerability. [Note, although AE concerns with antipsychotics are significant, other psychotropic alternatives may even be worse.]
- At doses used, efficacy favored olanzapine ~5mg/day and risperidone 1mg/day. Quetiapine dose ~50mg/day may have been too low.
- Side effects profiles will differ depending on agent and dose. Olanzapine at dose used was associated with worse tolerability.
- The trial may offer some insight regarding **potential advantages and disadvantages** of each AP:
  - Efficacy longest Tx duration: ⇨favours OLZ, RIS
  - Sedation: ⇨most with OLZ, QUE
  - Parkinsonism/EPS ⇨most with OLZ, RIS; least QUE
  - Confusion/mental status ⇨most with OLZ, RIS
  - Cognitive disturbance ⇨most with OLZ
  - Neurological composite ⇨ more with OLZ vs RIS [16]
  - Weight gain ⇨ most with OLZ, RIS
  - QUE may be considered for patients with concurrent sleep disturbance or for patients at increased risk for falls, Parkinsonian symptoms & EPS (but some anticholinergic effects)

AD:Alzheimer's disease ADAS-cog score:Alzheimer's Disease Assessment Scale – cognitive subscare **AP**:antipsychotic **BPRS**:Brief Psychiatric Rating Scale **CMAI**:Cohen-Mansfield Agitation Inventory **EPS**:extrapyramidal symptoms **MMSE**:Mini-Mental Status Exam **NPI**: Neuropsychiatric Inventory

See pg 2 on back or online for supplementry information.

RxFiles CATIE-AD Trial Summary: Supplement Page

Design: additional features

- **Patients eligible for 3 other Tx phases** if physician deemed lack of efficacy or tolerability from assigned Tx: Phase 2 from 2-12wks: randomized to different AP or citalopram; Phase 3 from wk 4: randomized, open Tx; Phase 4 "Open-Choice Phase" (anytime)
- **Primary endpoint:** time to D/C of Tx for any reason $_{\text{Phase 1.}}$
- **Secondary endpoints:** time to D/C of Tx for lack of efficacy $_{\text{Phase 1}}$; time to D/C of Tx for AE, intolerability, death $_{\text{Phase 1}}$; Clinical Global Impression of Change (CGIC) $_{\text{wk 12}}$: continued Tx with original Phase 1 study drug & at least minimal improvement on scale

RESULTS $^{\text{Phase 1 Only}}$: additional features

- **Primary endpoint:** (see Table I)
  - **NS among Tx groups**; NS median time to D/C - range: 5.3wks $_{\text{QUE}}$ to 8.1wks $_{\text{OLZ}}$, **D/C Tx in ~50% by 8 wks**
  - **Only 19% completed entire study while taking their intially assigned medication**[7]
- **Efficacy** $_{\text{based on time to D/C}}$: **favoured OLZ$_{\text{22.1 wks}}$, RIS$_{\text{26.7 wks}}$** vs. QUE$_{\text{9.1 wks}}$ & PL$_{\text{9 wks}}$
  - OLZ and RIS NI to each other; OLZ superior to QUE$_{\text{HR 0.63 (0.41-0.96)}}$
- **Tolerability** $_{\text{based on time to D/C due to AE, intolerability, or death}}$: **favoured PL**
  - Discontinuation rates: PL 5% vs. OLZ 25%$_{\text{NNH=5/9mos}}$, QUE 16%$_{\text{NNH=9/9mos}}$, RIS 18%$_{\text{NNH=8/9mos}}$; overall: 63% @12wks
- **CGIC:** NS among Tx groups
- 17% did not receive an AP: randomization to PL, citalopram, or open-choice AP other than assigned study medications [8]
- 43 (12%) received OLZ & QUE, 42 (12%) received OLZ & RIS, 24 (7%) received all 3 AP during trial follow-up[8]
- **Table 3: Adverse Event, Safety Outcomes**

No. (%)	**Olanzapine** (n=100)	**Quetiapine** (n=94)	**Risperidone (**n=85)	**Placebo** (n=142)
Any Serious AE	14 (14)	17 (18)	9 (11)	19 (13)
Sedation	24 **(24)**	21 **(22)**	13 (15)	7 (5)
Parkinsonism or EPS	12 **(12)**	2 (2)	10 **(12)**	1 (1)
% D/C due to EPS	*6* ***(6)***	*1 (1)*	*4* ***(5)***	*1 (1)*
Falls, fractures, injuries	17 (17)	7 (7)	10 (12)	21 (15)
Cerebrovascular event / TIA	2 (2)	1 (1)	1 (1)	1 (1)
Mortality (?CV $^{\text{QT prolongation}}$?Infection $^{\text{sedation} \rightarrow \text{aspiration}}$)	1 (1)	3 (3)	1 (1)	3 (2)
Cognitive Disturbance	5 **(5)**	0	1 (1)	1 (1)
Confusion / mental status Δ	18 **(18)**	6 (6)	9 **(11)**	7 (5)
Psychotic Symptoms	7 **(7)**	0	0	3 (2)
Weight ↑ >7% - no (%)	10/90 (11)	5/80 (6)	8/75 (11)	4/128 (3)
[Weight change lb/mo of Tx]	[1.0 ± 0.4] $_{\text{SS vs. PL}}$	[0.4 ± 0.6] $_{\text{SS vs. PL}}$	[0.7 ± 0.4] $_{\text{SS vs. PL}}$	[-0.9 ± 0.3]
Magnitude of gain$_{\text{12wks}}$ (lb)[8]	*1.4*	*1.7*	*1.2*	
Glucose Δ$_{\text{from baseline (mmol/L)}}$	0.62 ± 0.32	0.14 ± 0.36	0.31 ± 0.33	-0.07 ± 0.28
TC Δ$_{\text{from baseline (mmol/L)}}$	0.29 ± 0.12	-0.05 ± 0.13	-0.19 ± 0.13	-0.19 ± 0.11
TG Δ$_{\text{from baseline (mmol/L)}}$	0.23 ± 0.12	0.18 ± 0.13	0.01 ± 0.12	0.13 ± 0.11

- **Limited long-term role; ~80% DC Tx by 36wks**
- **Greater efficacy w/ OLZ & RIS; offset by ↑AEs, especially for OLZ**

COMMENTS:

- Quetiapine dose may have been too low; lack of efficacy versus other AP secondary to suboptimal dose?[9]
  - Some argue that optimal dose may be ~100mg/day based on an open-label study (n=10, 76 years, significant improvement in agitation subscale of NPI at 6 & 12 wks w/ mean QUE 100mg/day) [10]
  - However, more recent RCT of quetiapine 100mg/day$_{\text{n=26 (achieved by 88%)}}$ vs. placebo$_{\text{n=29}}$ did not find benefit for agitation $_{\text{CMAI at 6 or 26 wks}}$ using this suggested "optimal" dose[11] → **sedative only at this dose?**[12]
  - Rate of AE w/ QUE likely underestimated with dose used; negative benefit of QUE vs. PL also observed in more recent trial $_{\text{median dose: 200mg/day}}$[13]
- Lack of washout period was of concern to some
- Safety measures limited by short duration of Tx
  - High rate of discontinuation limits assessment of metabolic changes and incidence of stroke, mortality, and cognitive decline observed in other trials[7,11]
    - NB: MMSE scores did not worsen in the present trial however Ballard, et al.[11] demonstrated clinically significant cognitive decline $_{\text{SIB change >10 pts}}$ with QUE vs. PL over longer follow-up period $_{\text{6 & 26 wks}}$
- Knowledge of possible randomization to placebo may have influenced early D/C rates by study physicians by accelerating select patients into definitive active treatment[7]
- Primary outcome beneficial in assessing efficacy, safety, & tolerability into single global measure, however does not agree with Tx guidelines supporting reassessment & D/C after period of behavioural stability[9]
  - Endpoint suggested to be more clinically relevant in comparison to previous studies using behavioural rating scales[14]
  - NS findings may be secondary to small sample size and Tx duration too short to determine benefit
- Findings not generalizable to patients with DLB $_{\text{neuroleptic sensitivity}}$[15] or VD $_{\text{excluded from trial}}$; may not be generalizable to nursing home patients with more severe AD$_{\text{MMSE<10}}$ - earlier trial did not find benefit $_{\text{QUE vs. PL}}$ for agitation in severe AD pts & was associated with significant cognitive decline[12]
- Recent antipsychotic meta-analysis for off-label uses[16]

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