The First Approved Treatment for Agitation

Where do we go from here?

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Introduction

- Over 57.4m people worldwide have dementia, prevalence anticipated to double every 20 years
- Cognitive, behavioral, and psychological symptoms of dementia (BPSD) include anxiety, depression, and psychotic symptoms as well as behavioral issues
- As high as 70% of patients with Alzheimer's with BPSD
- Most complex, stressful, and costly aspects of care, lead to poor outcomes

Nichols, Emma et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health, Volume 7, Issue 2, e105 - e125

How to we address this? - Nonpharmacologic

- Training paid caregivers in communication, person-centered care skills or dementia care mapping
  - Goal is to communicate with people with dementia, to understand and fulfill their wishes and needs
  - Associated with 30% decrease in agitation
- Music therapy, sensory based activities reduce emergent agitation and decrease symptomatic agitation in care homes
- Needs more data: group activities, how these activities translate to own home
- Not effective: "therapeutic touch"

Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, et al. A systematic review of the effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. Health Technol Assess 2014;18(39)

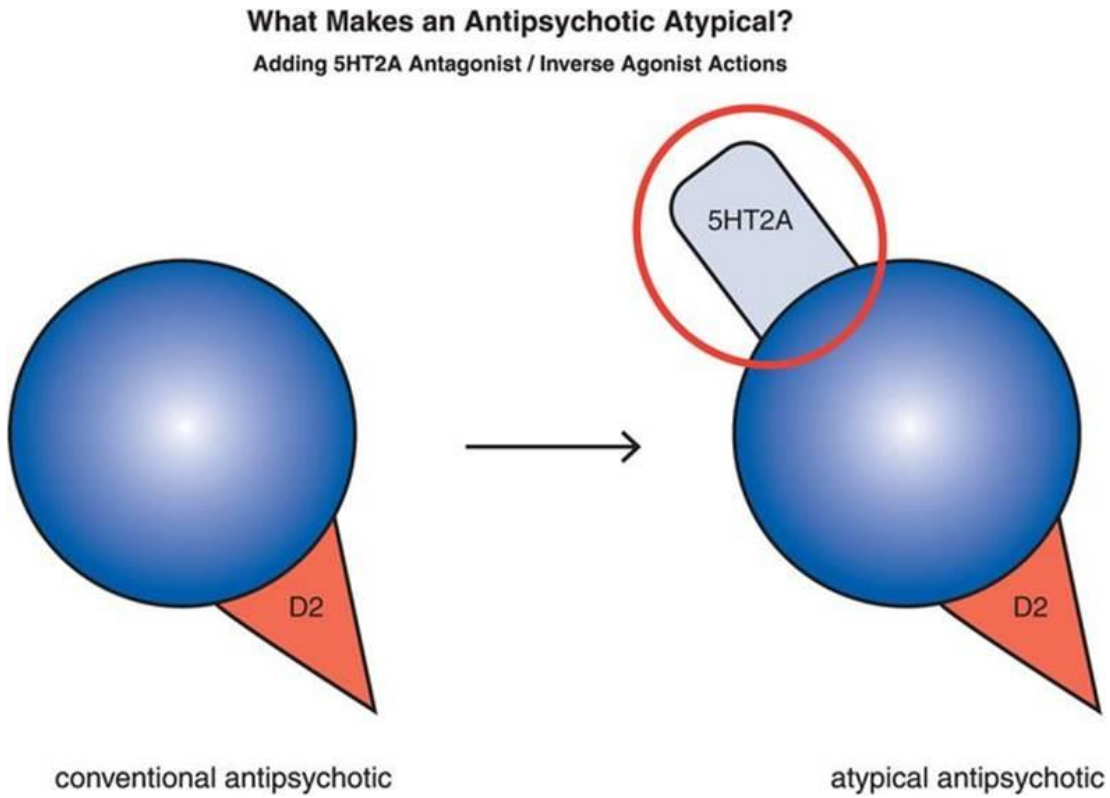
Where did we come from?

1990's shift from conventional to atypical antipsychotics

By 2001, more than 70% of US atypical antipsychotic prescriptions were for off label indications (dementia).

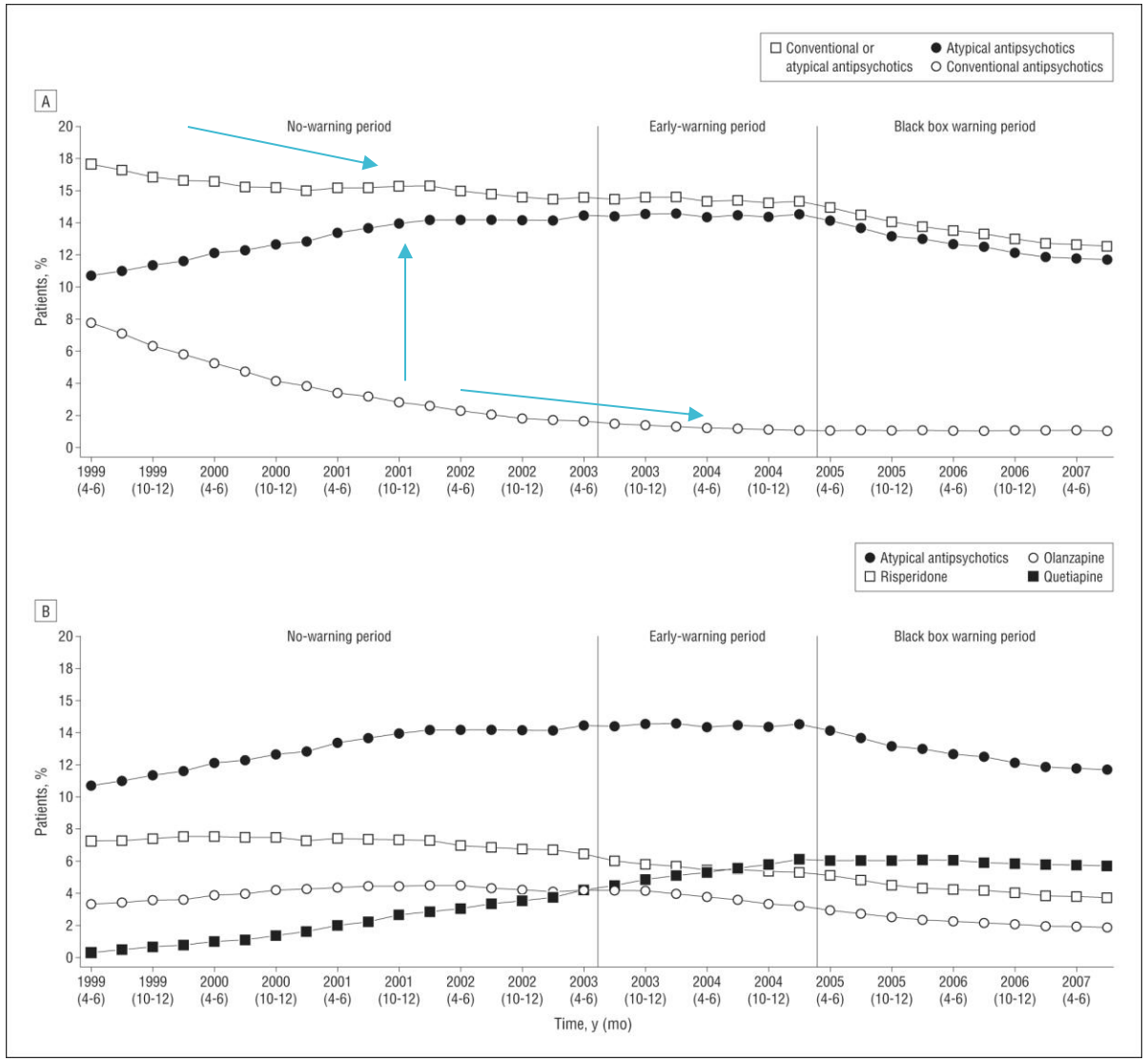
In 2005, FDA issues black box warning "treatment of behavioral disorders in elderly patients with dementia with atypical antipsychotic medications is associated with increased mortality"

Similar warning for conventional antipsychotics followed in 2008



Kales HC, Zivin K, Kim HM, et al. Trends in Antipsychotic Use in Dementia 1999-2007. Arch Gen Psychiatry. 2011;68(2):190–197. doi:10.1001/archgenpsychiatry.2010.200

Stahl, S. M. (2008). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications (3rd ed.). Cambridge University Press.



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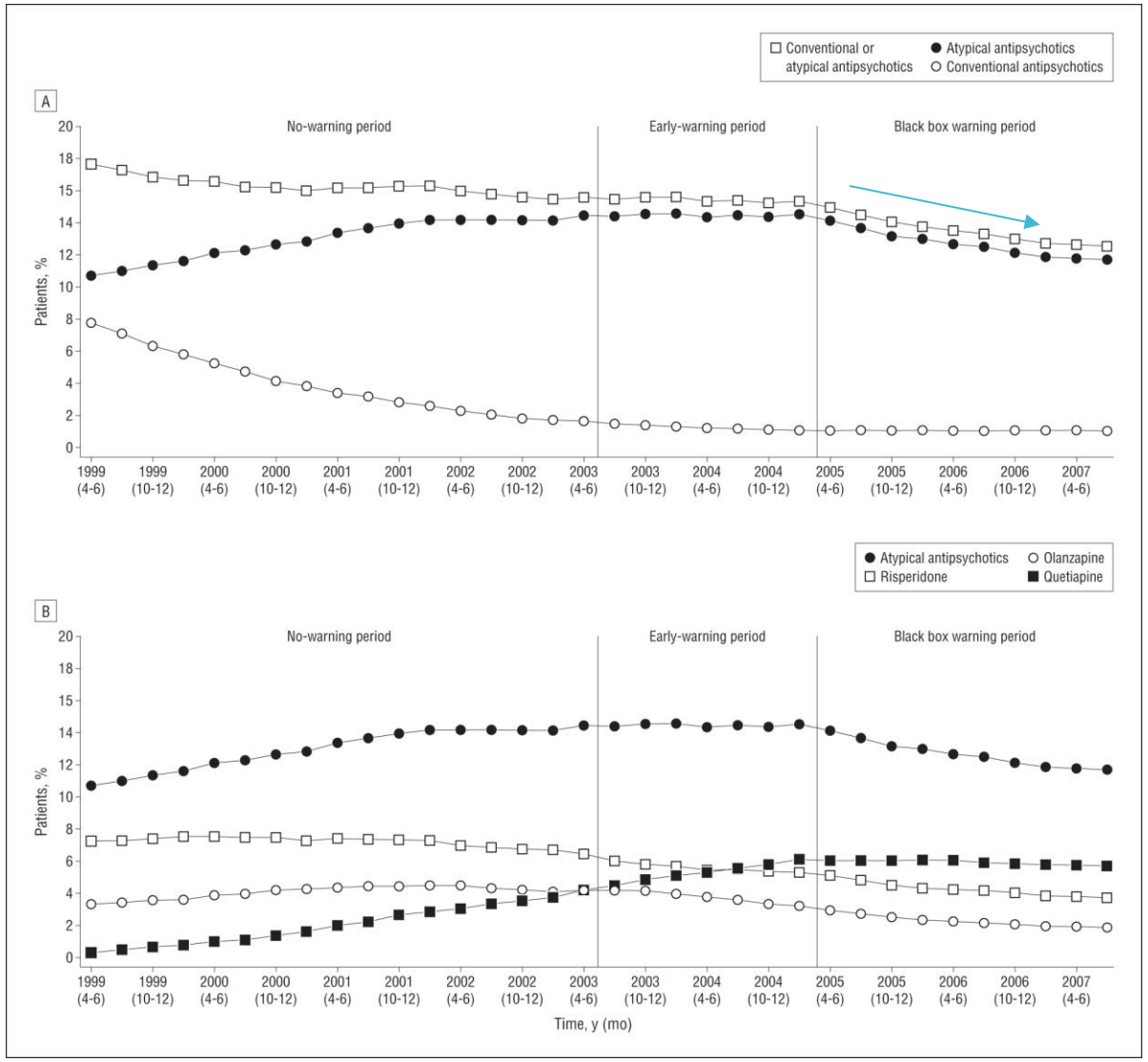

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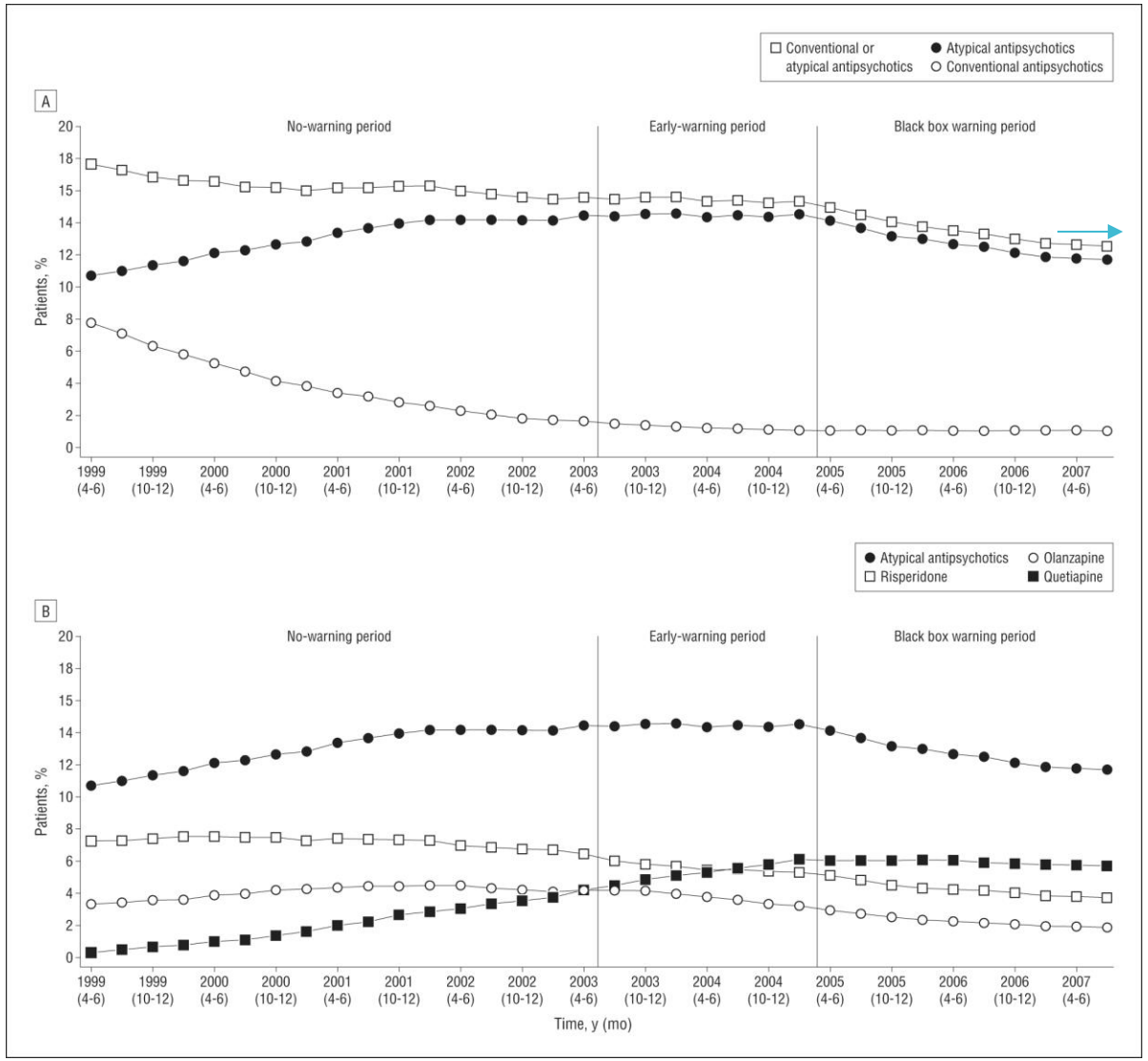


Kales HC, Zivin K, Kim HM, et al. Trends in Antipsychotic Use in Dementia 1999-2007. Arch Gen Psychiatry. 2011;68(2):190–197. doi:10.1001/archgenpsychiatry.2010.200

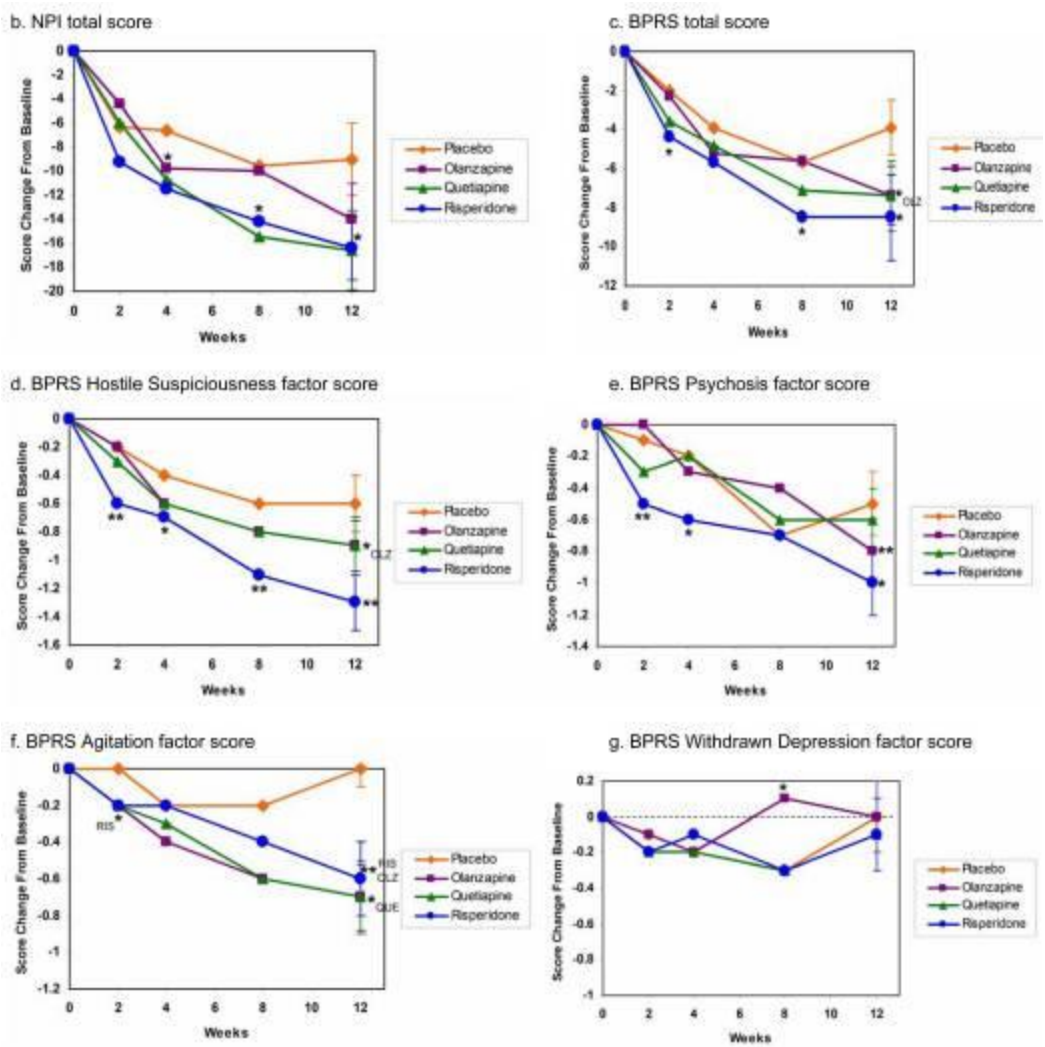
Where did we come from?

- Prevalence of antipsychotic drug use in dementia decreased from 31.3% in 2000 to 20.4% in 2012
- Decrease in anxiolytics, hypnotics/sedatives, but increase in antidepressants from 43.3%-53.8% from 2000 to 2012
- Treatment intensity among patients using antipsychotics increased, median number of defined daily doses increased from 22.2 to 42.0

Nørgaard A, Jensen-Dahm C, Gasse C, Hansen HV, Waldemar G. Time trends in antipsychotic drug use in patients with dementia: a nationwide study. J Alzheimers Dis. 2016;49(1):211-20. doi: 10.3233/JAD-150481. PMID: 26444790.

Where did we come from?

CATIE-AD trial: antipsychotics may be effective for particular symptoms such as anger, aggression, and paranoid but do not appear to improve patient functioning, care needs, or quality of life



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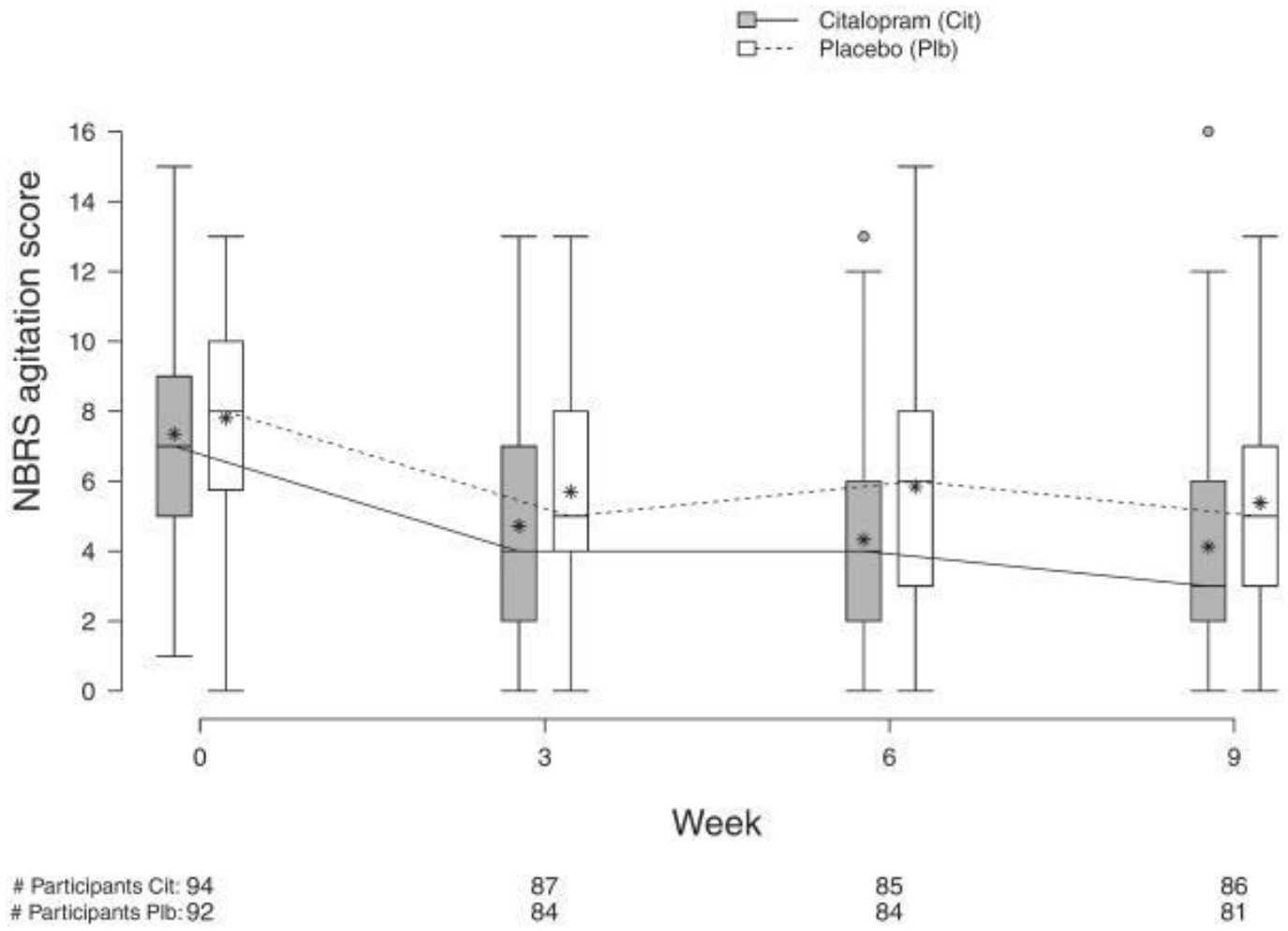
Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Lieberman JA, Schneider LS; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry. 2008 Jul;165(7):844-54. doi: 10.1176/appi.ajp.2008.07111779. Epub 2008 Jun 2. PMID: 18519523; PMCID: PMC2714365.



CitAD

2014 randomized, placebo controlled double blind parallel group trial from 2009 – 2013

Randomized to receive psychosocial intervention plus citalopram or placebo for 9 weeks

Citalopram doses began at 10mg with planned titration to 30mg over 3 weeks

Primary outcome: 18 point Neurobehavioral Rating Subscale and modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change

Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014 Feb 19;311(7):682-91. doi: 10.1001/jama.2014.93. PMID: 24549548; PMCID: PMC4086818.

Dextromethorphan

- ADVANCE-1: a phase 2/3, 5-week, multicenter, randomized double blind placebo-controlled trial
  - After 5 weeks, DM/BUP reduced CMAI scores by -15.4 points compared to buproprion alone
- ACCORD: phase 3, multicenter, randomized, double-blind, placebo-controlled trail conducting over 2 stages
  - Stage 1: compared to baseline mean CMAI score, DM/BUP showed significant mean CMAI score reductions of 6.7 points at week 1, 11 points at week 2, and 20.6points at week 3
  - Stage 2: responding patients randomized DM/BUP vs placebo for 26 weeks – DM/BUP showed significant delay in time to agitation relapse with 3.6 fold lower risk of relapse compared to placebo
- ADVANCE-2:anticipated to conclude by June 2025

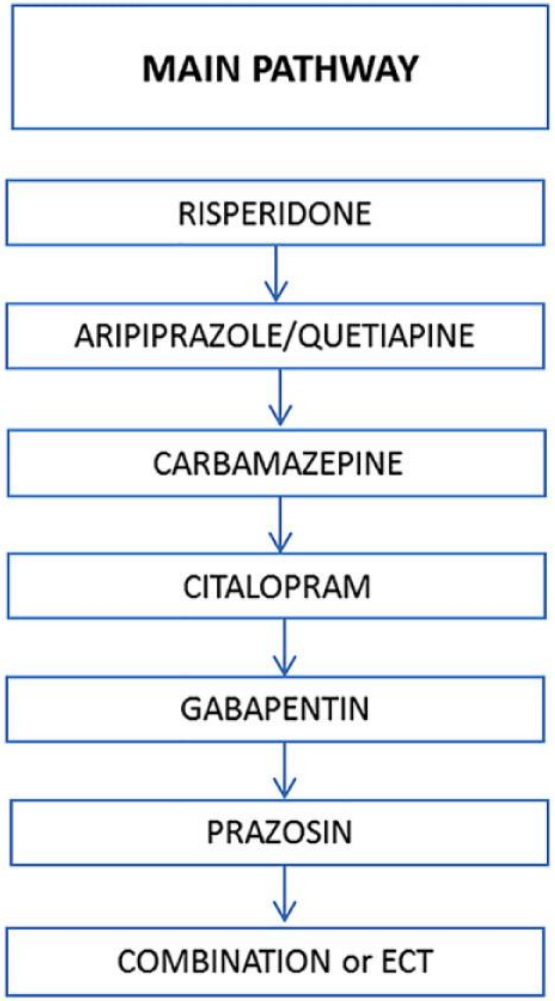
Lee D, Clark ED, Antonsdottir IM, Porsteinsson AP. A 2023 update on the advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother. 2023 Apr;24(6):691-703. doi: 10.1080/14656566.2023.2195539. Epub 2023 Mar 28. PMID: 36958727.

Less Promising

- Masupirdine
  - Orally active antagonist of serotonin 5-HT6 receptor – glutamate and GABA regulation and enhance cholinergic signaling
  - Animal models with pro-cognitive effects, however phase 3 clinical trials with no statistically significant cognitive effects
- Prazosin
  - Centrally acting α1-adrenoreceptor antagonist used for HTN, BPH, PTSD
  - Neurobiological studies suggest agitation related to dementia may involved enhanced responsiveness to NE at α1-adrenoreceptor
  - PEACE-AD – no statically significant difference between prazosin and placebo on ADCS-CGIC in agitation after 12 weeks

Lee D, Clark ED, Antonsdottir IM, Porsteinsson AP. A 2023 update on the advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother. 2023 Apr;24(6):691-703. doi: 10.1080/14656566.2023.2195539. Epub 2023 Mar 28. PMID: 36958727.

SUMMARY OF DRUGS



PRNS for Agitation/Aggression

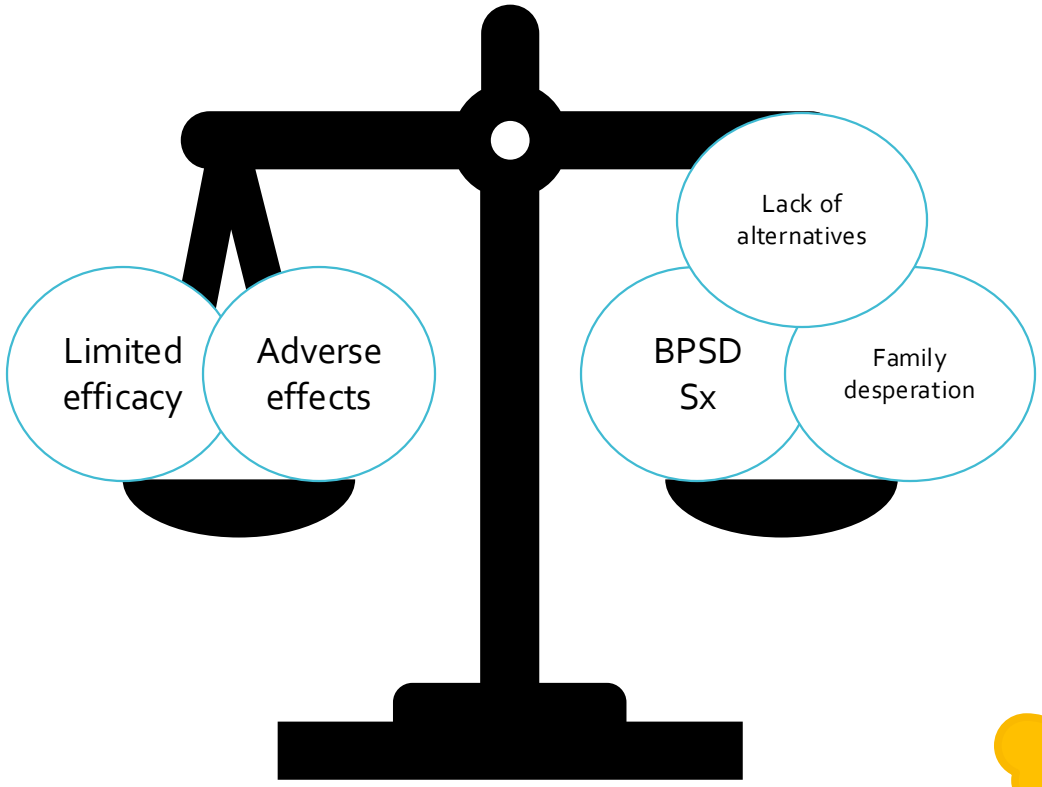
- TRAZODONE
- LORAZEPAM

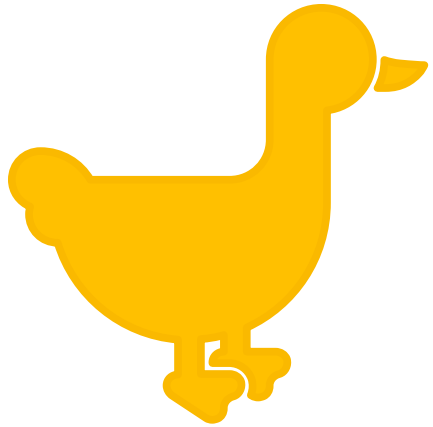
Alzheimer's Treatments

- ACETYLCHOLINESTERASE INHIBITORS
- MEMANTINE

Davies SJ, Burhan AM, Kim D, et al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. Journal of Psychopharmacology. 2018;32(5):509-523. doi:10.1177/0269881117744996

Where did we come from?





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Where are we now?

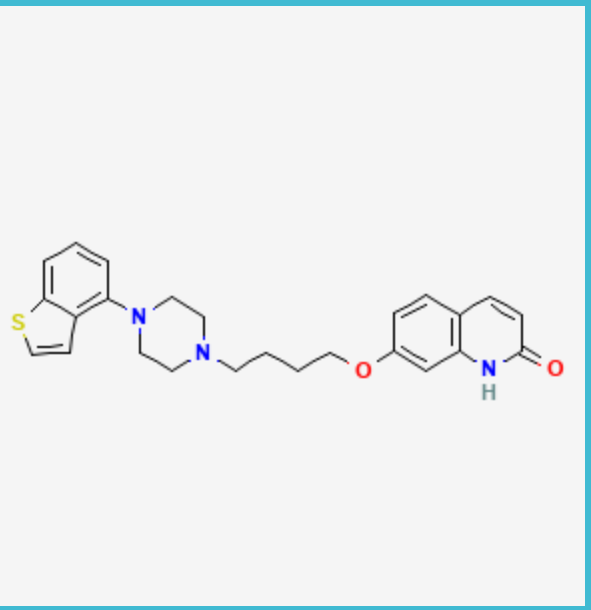
- On 5/11/2023, the FDA granted Otsuka Pharmaceutical Company Ltd., and Lundbeck Inc supplemental approval of Brexpiprazole, marketed as Rexulti, for treating agitation linked with Alzheimer's disease.
- Application was granted Fast Track Designation

Where are we now?

- Effectiveness: two 12 week randomized double-blind placebo-controlled fixed dose studies
- Inclusion: probable dx of AD, MMSE 5 to 22, exhibit type, frequency, and severity of agitation to require meds. Ranged from 51 to 90yo.
- 1st study: 1-2mg of Rexulti fixed dose
- 2nd study: 0.5-2mg of Rexulti flexible dose
- Primary endpoints: Cohen-Mansfield Agitation Inventory (CMAI) score at week 12 - statistically significant/clinically meaningful improvements in total CMAI scores compared to placebo

Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, Slomkowski M, Baker RA, McQuade RD, Cummings JL. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. Am J Geriatr Psychiatry. 2020 Apr;28(4):383-400. doi: 10.1016/j.jagp.2019.09.009. Epub 2019 Oct 1. PMID: 31708380.

Brexpiprazole



- Atypical antipsychotic FDA-approved for treatment of schizophrenia and as adjunctive with antidepressant for Major Depressive Disorder
- Partial agonist at 5-HT1a and D2 receptors, antagonist at 5-HT2a receptors
- Dosing per package insert: start at 0.5mg/day, increase dose on days 8-14 to 1mg daily, then on day 15mg to 2mg daily, max 3mg/day

Commissioner, O. of the. (n.d.). FDA approves first drug to treat agitation symptoms associated with dementia due to alzheimer's disease. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease

Cohen-Mansfield Agitation Inventory (CMAI)

Instructions: For each of the behaviors below, check the rating that indicates the average frequency of occurrence over the last 2 weeks.

Behavior	Never 1	Less Than Once a Week 2	Once or Twice a Week 3	Several Times a Week 4	Once or Twice a Day 5	Several Times a Day 6	Several Times an Hour 7
1. Hitting (including self)	❑	❑	❑	❑	❑	❑	❑
2. Kicking	❑	❑	❑	❑	❑	❑	❑
3. Grabbing onto people	❑	❑	❑	❑	❑	❑	❑
4. Pushing	❑	❑	❑	❑	❑	❑	❑
5. Throwing things	❑	❑	❑	❑	❑	❑	❑
6. Biting	❑	❑	❑	❑	❑	❑	❑
7. Scratching	❑	❑	❑	❑	❑	❑	❑
8. Spitting	❑	❑	❑	❑	❑	❑	❑
9. Hurt self or others	❑	❑	❑	❑	❑	❑	❑
10. Tearing things or destroying property	❑	❑	❑	❑	❑	❑	❑
11. Making physical sexual advances	❑	❑	❑	❑	❑	❑	❑
12. Paces, aimless wandering	❑	❑	❑	❑	❑	❑	❑
13. Inappropriate dress or disrobing	❑	❑	❑	❑	❑	❑	❑
14. Trying to get to a different place.	❑	❑	❑	❑	❑	❑	❑
15. Intentional falling	❑	❑	❑	❑	❑	❑	❑
16. Eating/drinking inappropriate substances	❑	❑	❑	❑	❑	❑	❑
17. Handling things inappropriately	❑	❑	❑	❑	❑	❑	❑
18. Hiding things	❑	❑	❑	❑	❑	❑	❑
19. Hoarding things	❑	❑	❑	❑	❑	❑	❑
20. Performing repetitious mannerisms	❑	❑	❑	❑	❑	❑	❑
21. General restlessness	❑	❑	❑	❑	❑	❑	❑
22. Screaming	❑	❑	❑	❑	❑	❑	❑
23. Making verbal sexual advances	❑	❑	❑	❑	❑	❑	❑
24. Cursing or verbal aggression	❑	❑	❑	❑	❑	❑	❑
25. Repetitive sentences or questions	❑	❑	❑	❑	❑	❑	❑
26. Strange noises (weird laughter or crying)	❑	❑	❑	❑	❑	❑	❑
27. Complaining	❑	❑	❑	❑	❑	❑	❑
28. Negativism	❑	❑	❑	❑	❑	❑	❑
29. Constant unwarranted request for attention or help	❑	❑	❑	❑	❑	❑	❑

Name of Rater:

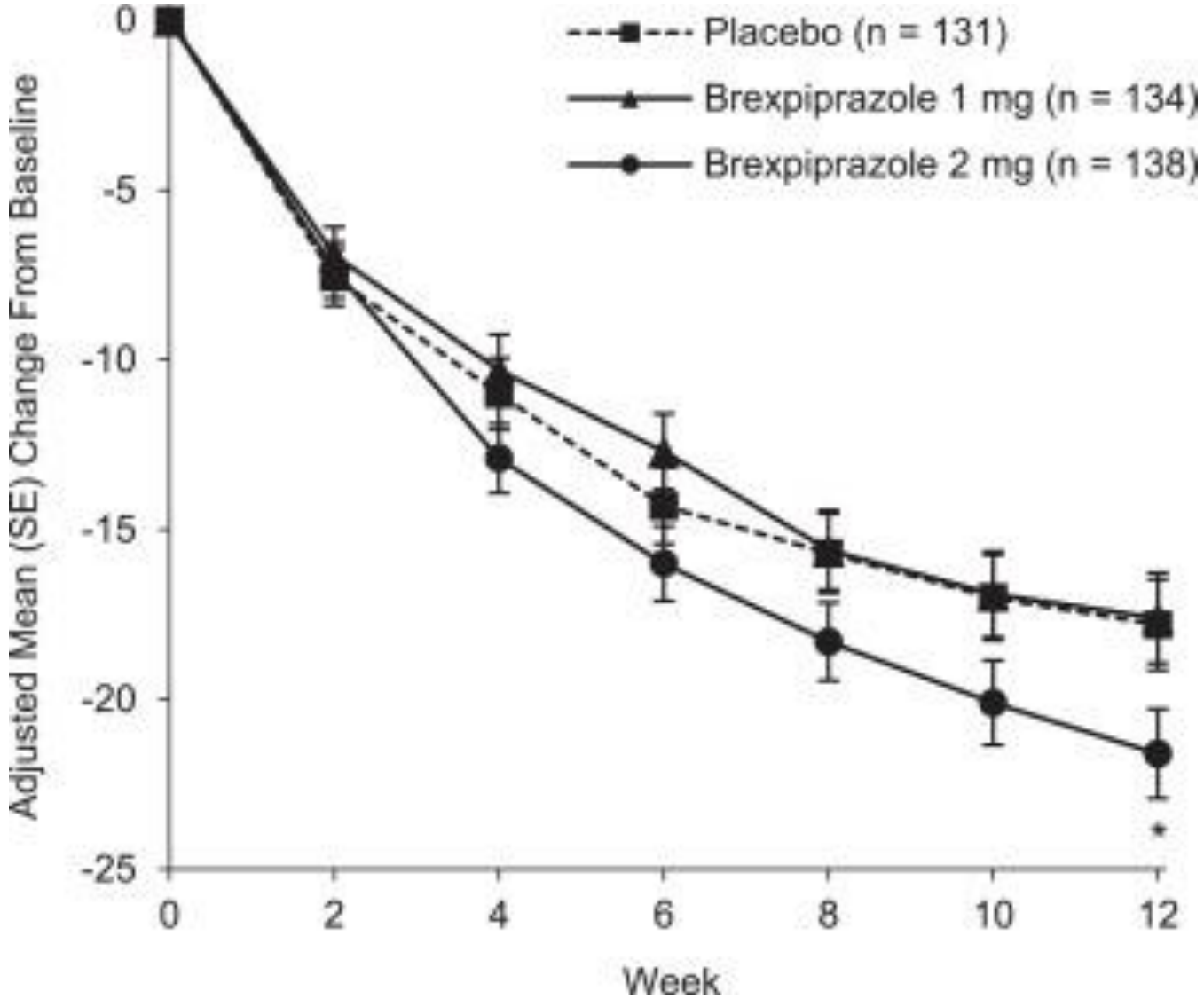
Name of Primary Caregiver/Informant:

Note: This is the nursing-home, long version of the Cohen-Mansfield Agitation Inventory. For definitions of the behaviors, administration, scoring information, and other versions, please consult the manual.

Primary endpoint

Cohen-Mansfield Agitation Inventory: caregivers assess the weekly frequency of 29 behaviors from a score of 1 to 7, resulting in scores ranging from 29 to 203. "Minimal clinically important difference" at 12 weeks on CMAI scale is 17 points (Mauleon, 2021)

-CMAI Total score change from baseline to week 12



Study 1

Brexpiprazole 2mg group demonstrated statistically significant improvement in CMAI Total score change from baseline to week 12 compared with placebo group. Brexpiprazole 1mg arm did not have meaningful separation.

Secondary endpoint (CGI-S score): brexpiprazole 2mg demonstrated numerical improvement, however not statistically significant

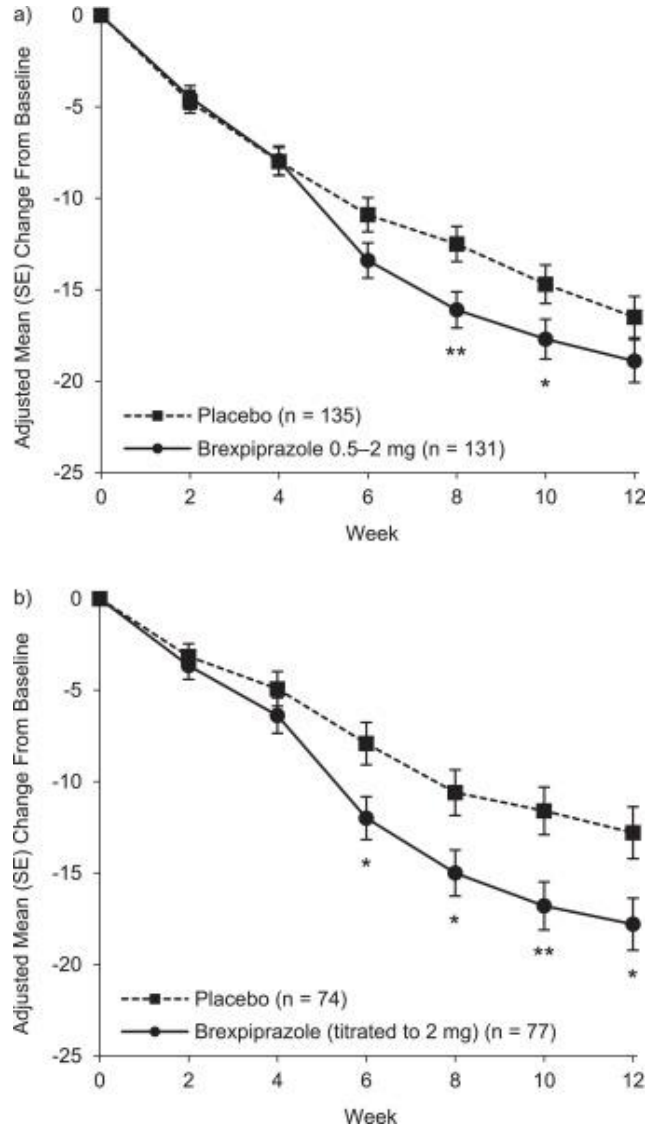
Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, Slomkowski M, Baker RA, McQuade RD, Cummings JL. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. Am J Geriatr Psychiatry. 2020 Apr;28(4):383-400. doi: 10.1016/j.jagp.2019.09.009. Epub 2019 Oct 1. PMID: 31708380.

Study 2

Brexpiprazole 0.5-2mg did not achieve statistical superiority compared to placebo.

In post hoc efficacy analysis, the subgroup of patients titrated to maximum brexpiprazole dose (2mg) at week 4 showed improvement in CMAI total score compared with placebo

Secondary endpoint: subgroup titrated to brexpiprazole 2mg at Week 4 showed greater improvement in CGI-S score than placebo



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WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

Rexulti will retain the Boxed Warning for medications in this class that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

4x increase in mortality rate (compared to 1.6-1.7x for other SGA)

Safety

1) Incidence of treatment emergent adverse effects over 12 weeks was 65% in brexpiprazole 2mg group, 49% in brexpiprazole 0.5-1mg group, and 45.9% in placebo group

2) No difference between brexpiprazole 0.5-2mg group and placebo group

Most common side effects: headache, dizziness, urinary tract infection, nasopharyngitis, and sleep disturbances (both somnolence and insomnia). Serious AE: seizure

Response

Alliance for Aging Research, Leaders Engage on Alzheimer's Disease, Us against Alzheimers urged FDA to approved brexpiprazole

Potentially fueled by commercial interest

- LEAD is a "coalition of more than 200 organization" including Otsuka
- Alliance for Aging Research receives funding from Otsuka, and amongst its 17 partners included representatives from Otsuka and four other drug companies

Clinicians' response likely vary according to their current beliefs about prescribing antipsychotics.

FDA approval could undermine message from CMS

BMJ. (2023, August 18). Alarm as FDA fast-tracks first antipsychotic for dementia agitation | BMJ. https://www.bmj.com/company/newsroom/alarm-as-fda-fast-tracks-first-antipsychotic-drug-for-agitation-in-dementia/

Controversy

- $1400/month
- Concern that FDA's decision may reverse years of effort by Centers of Medicare and Medicaid Services to reduce widespread off-label use of antipsychotics in residential care homes
- Same "boxed warning" about increased risk of death. In three preapproved trials, FDA concluded death rate was 4x higher in those given brexpiprazole compared to those given placebo
- Maximum 5.4 point improvement on 174 point CMAI scale, far short of 17 points considered clinically important

BMJ. (2023, August 18). Alarm as FDA fast-tracks first antipsychotic for dementia agitation | BMJ. https://www.bmj.com/company/newsroom/alarm-as-fda-fast-tracks-first-antipsychotic-drug-for-agitation-in-dementia/

De Mauleon A, Ismail Z, Rosenberg P, Miller D, Cantet C, O'Gorman C, Vellas B, Lyketsos C, Soto M. Agitation in Alzheimer's disease: Novel outcome measures reflecting the International Psychogeriatric Association (IPA) agitation criteria. Alzheimers Dement. 2021 Oct;17(10):1687-1697. doi: 10.1002/alz.12335. Epub 2021 Jun 16. PMID: 34132461; PMCID: PMC9292260.

Controversy

Results of Study 213 were unusual: brexpiprazole produced no benefit at US sites, which enrolled 44% of patients.

- The reported 5.3 point benefit was the result of a nine point drug-placebo difference in patient across five easter European country and Spain. No benefit was seen at US sites
- 9 point placebo-drug difference was an outlier compared to results in the other two phase 3 trials and earlier trials of other atypical antipsychotics (i.e. risperidone and aripiprazole in 2005 ranged from 2.3 to 4.4 points)

Lower Standards? Some disappointment in additional indication based on weak data

Whitaker R. How the FDA approved an antipsychotic that failed to show a meaningful benefit but raised the risk of death. BMJ. 2023 Aug 17;382:1801. doi: 10.1136/bmj.p1801. PMID: 37591522.

More questions

- Was there evidence that brexpiprazole provided clinically meaningful benefit?
- Was there evidence that its risk-benefit profile was superior to antipsychotics that are currently prescribed off-label?
- Was the lack of an effect at the US sites important?

Bottom Line

- Minimal clinically important difference was not easy to determine – hard to tell if it crossed the threshold
- Variability in presentation and severity of agitation – need for individualized risk-benefit evaluation

Table 1

Summary of the potential druggable targets that might be suitable for pharmacological modulation of selected behavioral and psychological symptoms of dementia (BPSD): psychosis, aggression, and agitation

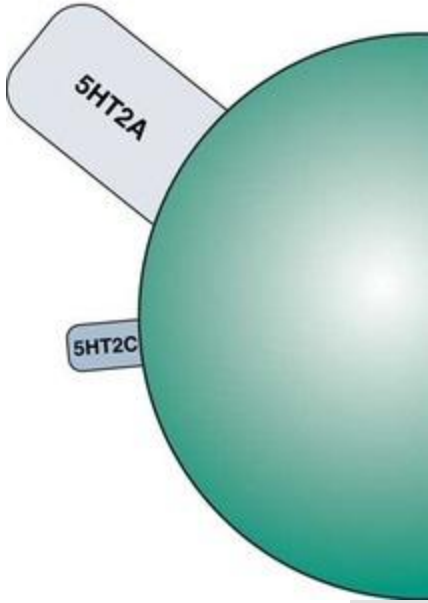
Matching with BPSD pathology		**Indicated by experimental studies**	
Target	**Pharmacological activity**	**Target**	**Pharmacological activity**
Serotonin 5-HT_{2A} receptors	Antipsychotic, antiaggressive	Muscarinic M_1/M_2 receptors	Antipsychotic, procognitive
Serotonin 5-HT_{1A} receptors	Antiaggressive	Cannabinoid receptor CB_1	Antiaggressive
Serotonin transporter	Antiaggressive	Metabotrophic glutamate 2 receptor (mGlu2)	Antipsychotic
Dopamine D_1, D_2 receptors	Antipsychotic, antiaggressive	Serotonin 5-HT_6 receptors	Procognitive, anxiolytic
Alpha-1 adrenoreceptor	Antiaggressive		

Future Directions

Marcinkowska M, Śniecikowska J, Fajkis N, Paśko P, Franczyk W, Kołaczkowski M. Management of Dementia-Related Psychosis, Agitation and Aggression: A Review of the Pharmacology and Clinical Effects of Potential Drug Candidates. CNS Drugs. 2020 Mar;34(3):243-268. doi: 10.1007/s40263-020-00707-7. PMID: 32052375; PMCID: PMC7048860.

Future Directions – Serotonin

- In dementia, 5HT2A receptor binding is decreased, reduced density of 5HT2A receptors in prefrontal cortex. Polymorphism of 5-HT2A receptors associated with increased risk of hallucinations/aggression, particularly those in LBD (visual)
  - compounds like pimavanserin, a 5-HT2A receptor inverse agonist, that preferentially block 5-HT2A
  - effective in reducing delusions/hallucinations in PD, being evaluated for efficacy in other psychotic disorders, including AD-related psychosis
- Serotonin transporter (SERT) polymorphism a/w aggressive behavior in patient with AD
- Decreased density of 5-HT1A receptors in the cortex have been linked with onset of aggressive behavior in patients with AD



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Stay Tuned

- Escitalopram – S-CitAD study, a phase 3 multicenter randomized, sequential-phase trial
- Cannabinoid CB1 receptor
- Glutamate receptors and N-methyl-D-aspartate receptors
- Muscarinic receptors M1/M4
- 5-HT6 receptor antagonists
- Polymorphisms in dopamine D1 and D3 receptors a/w dementia-related psychosis and aggression

Marcinkowska M, Śniecikowska J, Fajkis N, Paśko P, Franczyk W, Kołaczkowski M. Management of Dementia-Related Psychosis, Agitation and Aggression: A Review of the Pharmacology and Clinical Effects of Potential Drug Candidates. CNS Drugs. 2020 Mar;34(3):243-268. doi: 10.1007/s40263-020-00707-7. PMID: 32052375; PMCID: PMC7048860.

Summary

- Reviewed the landscape of treatment options for agitation in Alzheimer's disease
- Described the safety and efficacy of recently approved treatments for agitation in Alzheimer's disease
- Explored additional targets and candidates for neuropsychiatric treatments for dementia

References

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Thank you!