

Clearing the Confusion?

Use of Trazodone for the Behavioural and Psychological Symptoms of Dementia

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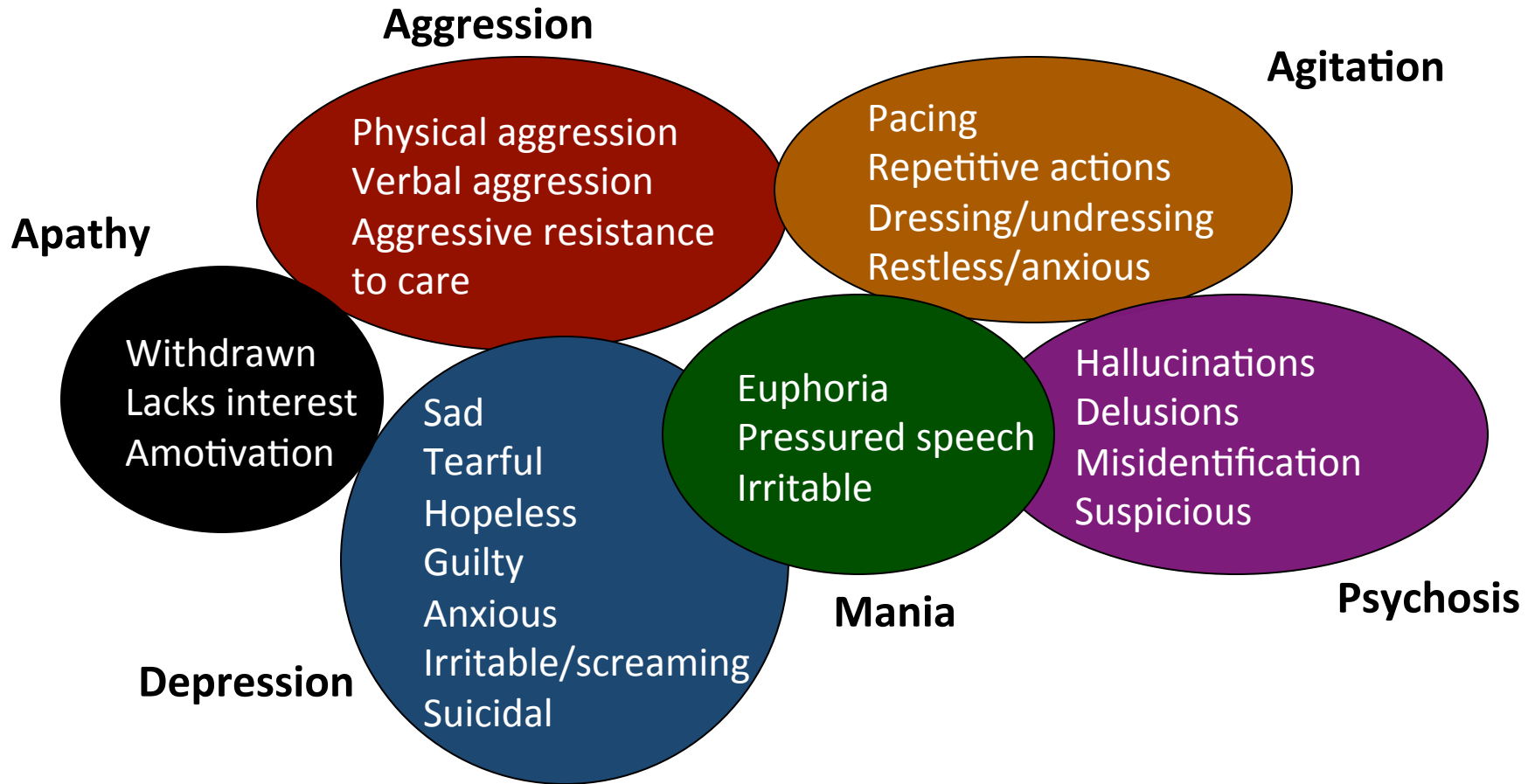
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Behavioural and Psychological Symptoms of Dementia (BPSD)

- Refers to symptoms of disturbed perception, thought content, mood or behaviour frequently occurring in patients with dementia
- ~83% of patients with dementia demonstrate psychopathology
- Pathophysiology is multi-factorial
 - Genetics
 - Polymorphism of dopamine and serotonin receptor genes
 - Neurofibrillary tangles

BPSD Symptom Clusters



Approach to Managing BPSD

- Determining target behaviours
- Identification of causes and triggers
- The ABC model (Antecedents, Behaviour, Consequences) has been proposed to individualize management
- Rule out/correct reversible causes

Non-Pharmacological Therapy

- 1st line management of most symptoms of BPSD
- Should also be used in combination with pharmacologic therapy
- Providing structure, involving relatives in care planning, involving patient in calming activities (listening to music, going for a walk) can lead to reduction in agitation

Pharmacological Therapy

- Cholinesterase inhibitors
- Memantine
- Anti-psychotics
- Anti-depressants
- Anti-convulsants
- Sedative/hypnotics

Why Trazodone?

- Mild effect on presynaptic serotonin reuptake but acts as an antagonist at postsynaptic serotonergic receptors
- More desirable side effect profile compared to other therapeutic alternatives

Clinical Question

P	Patients diagnosed with dementia and BPSD
I	Trazodone
C	Antidepressants, antipsychotics, cholinesterase inhibitors, memantine, anticonvulsants, benzodiazepines or placebo
O	Improvement in agitation, aggression, mania, depression, psychosis, apathy or sleep disturbances

Search Strategy

Databases	PubMed, EMBASE, PsycINFO, Web of Science, International Pharmaceutical Abstracts, Google Scholar, clinicaltrials.gov
Keywords	Trazodone, Dementia, Behavioural and Psychological Symptoms of Dementia, BPSD
Limits	Humans, English
Results	<ul style="list-style-type: none">- 4 RCTs- 2 Cochrane reviews

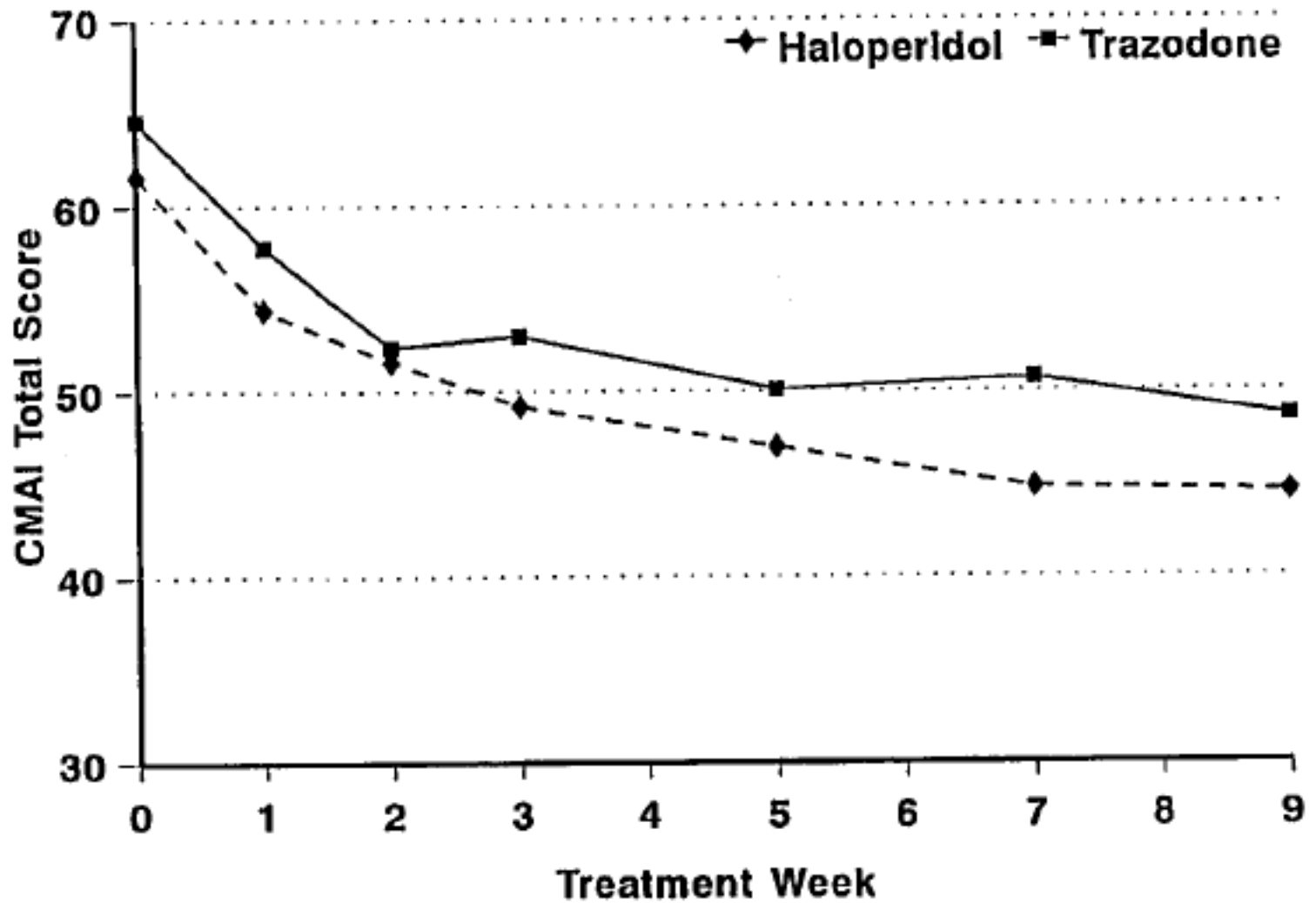
Sultzer et al (1997)

D	9 week randomized, double blind trial
P (n=28)	<ul style="list-style-type: none">- Patients who met diagnostic criteria for a specific dementia subtype and exhibited agitated behaviour- CMAI total score of at least 41 or an individual item score of at least 6- Recruited from Geropsychiatric Unit and Dementia Clinic at the Veterans Affairs Medical Center
I	Trazodone 50-100mg daily, increased to a max of 250mg
C	Haloperidol 1-2mg daily, increased to a max of 5mg
O	<ul style="list-style-type: none">- Behavioural measures included CMAI, CGI and OAS- Cognition assessed by MMSE- Measurement of ADRs

Baseline Characteristics

	Haloperidol (n=14)	Trazodone (n=14)
Age, yrs	72.1 ± 6.8	72.4 ± 7.0
Dementia duration, yrs	5.6 ± 3.0	4.7 ± 3.0
MMSE score, baseline	10.1 ± 6.8	11.9 ± 7.3
Dementia subtype (#)	<ul style="list-style-type: none"> - Probable AD (8) - Possible AD (1) - Vascular dementia (2) - Head trauma (1) - Mixed etiology (2) 	<ul style="list-style-type: none"> - Probable AD (5) - Possible AD (1) - Vascular dementia (3) - Mixed etiology (5)
CMAI total score, baseline	61.6 ± 12.2	64.6 ± 13.7
Medication dose during trial	2.5 ± 1.7	218.0 ± 65

Results



Results

	Treatment Week						
	Baseline	1	2	3	5	7	9
Subjects "much" or "very much improved" on CGI, %							
Haloperidol	—	21	36	57	36	50	57
Trazodone	—	14	36	43	43	50	71
OAS total score, mean ± SD							
Haloperidol	3.1 ± 1.9	1.6 ± 1.6	1.4 ± 1.3	0.8 ± 0.8	1.1 ± 1.4	0.9 ± 1.2	0.9 ± 1.1
Trazodone	1.6 ± 2.0	1.0 ± 1.5	0.4 ± 0.6	0.3 ± 0.5	0.5 ± 0.9	0.6 ± 0.9	0.4 ± 0.6

Results

- Behaviours responding preferentially to haloperidol
 - Pacing, restlessness, trying to get out of the building and unwarranted accusations
- Behaviours responding preferentially to trazodone
 - Repetitive mannerisms, repetitive sentences, cursing/verbal aggression, negativism/opposition to assistance

Adverse Effects

Haloperidol (n=14)	Trazodone (n=14)
<p>7 patients developed ADRs that included:</p> <ul style="list-style-type: none">- Sedation- Balance problems- Rigidity- Weakness- Incoordination- Skin rash <p>2 patients developed akathisia</p>	<ul style="list-style-type: none">- Sedation (1)- Imbalance (1)

Critique

- Small sample size
- Very specific patient population
 - Male veterans
- Heterogeneity between patients
 - Dementia subtype
 - Variety of agitated behaviours

Teri et al (2000)

D	16 week randomized, placebo-controlled multicenter trial
P (n=149)	<ul style="list-style-type: none">- Outpatients diagnosed with Alzheimer's disease- At least a two week history of two or more agitated behaviours occurring at least once weekly
I	Trazodone 50-300mg daily Haloperidol 0.5-3mg daily Behavioural management techniques (BMT)
C	Placebo
O	<p><u>Primary:</u></p> <ul style="list-style-type: none">- ADCS Clinical Global Impression of Change (CGIC) <p><u>Secondary:</u></p> <ul style="list-style-type: none">- Patient agitation and behavioural disturbance (CMAI)- Patient functional disturbance (IADL)- Cognitive function (MMSE)- Caregiver burden and reactivity to disruptive behaviours (SCB)

Baseline Characteristics

	BMT (n=41)	Haloperidol (n=34)	Trazodone (n=37)	Placebo (n=36)
Age, yrs	74.8 ± 8.4	75.3 ± 6.9	73.2 ± 6.6	75.8 ± 6.2
Female gender (%)	22 (54)	20 (59)	15 (41)	24 (67)
Caucasian ethnicity (%)	36 (88)	31 (91)	29 (78)	31 (86)
Dementia duration, yrs	4.7 ± 2.6	5.4 ± 3.8	5.1 ± 3.4	5.2 ± 3.2
MMSE score	12 ± 7	13 ± 8	14 ± 7	13 ± 8
Mean dose (mg/day)	8 sessions wkly, then 3 sessions biwkly	1.8 (0-3)	200 (50-300)	-

Results

Table 2 Primary outcome: ADCS-CGIC by treatment arm

Outcome	Behavior management techniques, n = 41	Haloperidol, n = 34	Trazodone, n = 37	Placebo, n = 36
Improved	13 (32)	11 (32)	15 (41)	11 (31)
No change	8 (20)	7 (21)	5 (14)	10 (28)
Worse	20 (49)	16 (47)	17 (46)	15 (42)

Values are n (%).

- No difference in ADCS-CGIC scores when BMT, haloperidol and trazodone were each compared to placebo ($p=0.65, 0.81, 0.99$)
- Comparison between active groups (BMT-haloperidol, BMT-trazodone, haloperidol-trazodone) were also non-significant ($p=0.86, 0.52, 0.75$)

Results

- Patient agitation – CMAI
 - No difference between groups
- Patient functional disturbance – ADL/IADLs
 - Patients on active medication were worse compared with placebo ($p < 0.05$)
- Cognitive function – MMSE
 - Trazodone associated with significantly worse change in MMSE compared with BMT (-1.97 ± 3.15 vs. -0.05 ± 2.58 , $p < 0.05$)
- Caregiver burden – SCB
 - No difference between groups

Adverse Effects

Adverse event	Behavior management techniques, Haloperidol, Trazodone, Placebo,			
	n = 41	n = 34	n = 37	n = 36
Drooling	7	7	0	0
Parkinsonian gait*	0	22	12	7
Dry mouth	4	26	16	13
Dizziness	4	7	16	7
Akathisia	4	11	3	10
Rigidity	11	33	9	13
Dyskinesia	7	7	0	13
Drowsiness	11	30	16	13
Bradykinesia†	0	33	16	20
Tremor	11	26	12	13
Fatigue	17	56	12	17

Critique

- Baseline agitation scores not reported
- No information provided about medication use prior to study entry
- Large drop-out in each study arm
- Study was conducted before cholinesterase inhibitors were routinely used in dementia

Does trazodone have a role in dementia at all?

Frontotemporal dementia: a randomised, controlled trial with trazodone.

Lebert et al. Dement Geriatr Cogn Disord 2004; 17(4): 355-9

- Trazodone 50-300mg daily significantly decreased neuropsychiatric inventory scores in all patients at 12 weeks ($p=0.028$). A decrease in NPI scores of 50% was observed in 10 out of 26 patients.

Trazodone Improves Sleep Parameters in Alzheimer Disease Patients: A Randomized, Double-Blind, and Placebo-Controlled Study.

Camargos EF et al. Am J Geriatr Psychiatry 2014

- Trazodone 50mg at bedtime improved duration of sleep by 42.5 mins in patients with AD and sleep disturbances compared to placebo

Conclusion

- No difference between trazodone and haloperidol in CMAI scores
- No difference between BMT, haloperidol or trazodone vs. placebo in CGIC scores
- Trazodone MAY have a role in neuropsychiatric symptoms in patients with FTD or in sleep disorders in patients with AD

Questions?

