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Enclosure:

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Treatment Patterns of Agitation associated with Alzheimer's Dementia (AAD) Patients in Canada

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Background

- Agitation associated with Alzheimer's dementia (AAD) is a challenging behavioral and psychological feature of Alzheimer's dementia characterized by excessive motor activity, verbal aggression, and/or physical aggression[1].
- Affecting up to 90% of people with Alzheimer's dementia, AAD is linked with greater caregiver burden, morbidity, and mortality[2,3].
- Although evidence supports the efficacy of specific therapies for treating AAD, many unapproved drugs or with variable risk/benefit profile are still being used[4]
- Treatment standards vary due to the lack of a unified understanding of agitation across clinicians and the paucity of approved AAD treatments and therapeutic strategies[3].
- To gain insights into clinical practice, we examined the clinician's treatment patterns of patients with AAD in Canada.

Methods

- This was a retrospective cohort study using public drug plan claims data from Ontario and New Brunswick, Canada.
- An indication algorithm was developed with a clinical expert to identify AAD through prescription claims for cognitive enhancers (cholinesterase inhibitors and memantine) and medications commonly used off-label to treat AAD symptoms (anticonvulsants [AC], antidepressants [ADT], antipsychotics [AP], benzodiazepines [benzo]).
- The study covered a twenty-year period (from 2003-2023).
- Inferred patients with AAD were identified between 2011-2018, indexed on the date of their first AC/ADT/AP/benzo and followed until their fourth line of therapy (4L).
- Using descriptive analyses this study explored lines of therapy, persistence, adherence, and dosing patterns.
- The first line of therapy (1L) was the first claim for AC/ADT/AP/benzo and any subsequent claims within 10 days.
- A 60-day grace period between prescriptions (in addition to days supply) determined if a patient was still using the same treatment.
- Any change (addition, reduction, switch, or restart) from 1L was considered a new line of therapy.
- Lines of therapy had to be at least 10 days long.

Results

- 23,732 inferred patients with AAD were identified (**Figure 1**), mostly from Ontario (98.7%), with a median (IQR) age of 80 (11) years (**Table 1**).
- Most of the cohort (70%) was followed until the end of their 4L therapy.
- The proportion of patients with AAD in a long-term care setting increased with greater lines of treatment going from 14% (1L) to 54% (4L) (**Figure 2**).
- Patients with AAD were treated with a wide range of therapies, with over 500 to 2000 unique combinations observed across 1L – 4L, respectively. For simplicity, analyses are provided only for the top five or ten therapies across each line of therapy.
- Some medications and their combinations consistently ranked among the top ten most commonly prescribed therapies: citalopram, escitalopram, gabapentin, lorazepam, mirtazapine, pregabalin, quetiapine, risperidone, sertraline, and trazodone (**Figure 3**).
- The top ten therapies accounted for 73% of all 1L treatment approaches.
- Of the 1L therapies, risperidone, the only approved medication to manage aggression or psychotic symptoms in patients with Alzheimer's dementia at the time of the study, accounted for 7.2% of claims, ranking as the 6th most commonly used therapy.
- Trazodone remained the most common therapy for patients with AAD. However, it had one of the lowest persistence rates among antidepressants.
- The highest proportion of patients remained on their 3L–4L after one year (**Figure 4**).
- Most cases (≥80%) were adherent to medications across all lines of therapy
- Average daily doses for the therapies were lower than those described in the product monographs.

CONCLUSIONS

- There is considerable variability in AAD-related treatment approaches among Canadian clinicians.
- Persistence declined in the first month of treatment, suggesting that medication may be used as needed or discontinued if ineffective. However, the increased persistence in 3L – 4L therapies suggests physicians are exhausting available treatment options.
- Our findings highlight the need for more evidence on treatments indicated for AAD, and increased education to facilitate evidence-based clinical practice.

References

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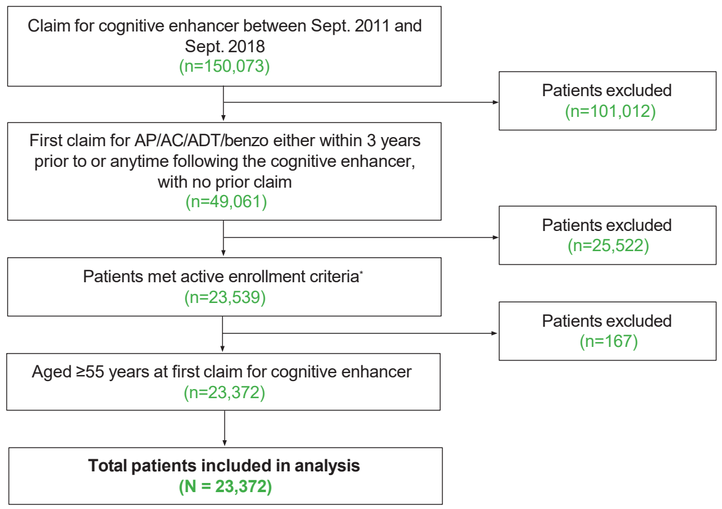
Figure 1. Patient Selection Flow.



* included data checks for age being >1 and <120 years old.
AP: antipsychotics; AC: anticonvulsants; ADT: antidepressants; benzo: benzodiazepines

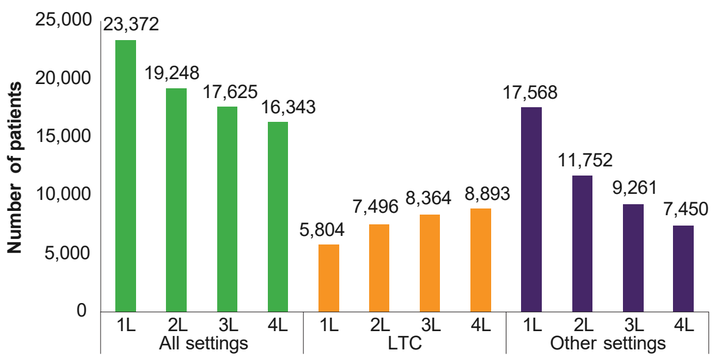
Table 1. Demographic characteristics of the study cohort at index.

Demographics	N = 23,372
Age≠	
Median (IQR)	80 (11)
≤54 years	15 (0.06%)
55 – 65 years	1,258 (5.4%)
66 – 75 years	5,960 (25.5%)
≥76 years	16,139 (69.1%)
Gender	
Female	13,133 (56.2%)
Province*	
West	<6 (0.01%)
Ontario	23,079 (98.7%)
New Brunswick	290 (1.2%)
Others	<6 (0.01%)
Prescribing physician^	
GP/FM	17,817 (76.2%)
Geriatrician	1,951 (8.4%)
Neurologist	794 (3.4%)
Other	2,810 (12.0%)
Payer	
Ontario Drug Benefit (LTC)	3,372 (14.4%)
Ontario Drug Benefit (Other)	19,710 (84.3%)
New Brunswick Drug Program	290 (1.2%)

≠Age was reported at index date
* Specifies the provincial location of the pharmacy claim; the payer for the claim remains either the ON or NB public plans; West includes BC, AB, SK, and MB; Others includes QC, NS, PEI, and NL
^ Only the top 3 prescribing specialties are described, with all others (including missing) aggregated into "Others"
GP/FM: general practitioner/family medicine; LTC: long-term care

Figure 2. Number of patients per setting followed from 1L – 4L therapies.

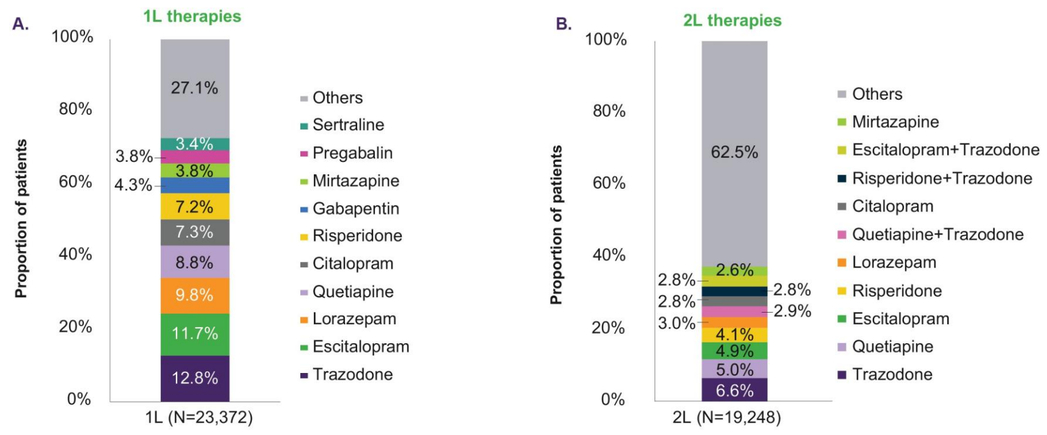
All non-LTC settings are grouped under "Other". Patients were classified based on the predominant setting of their claims within each line of therapy.



LTC: long-term care
1L-4L: first to fourth line of therapy

Figure 3. Therapies used by patients across 1L – 4L therapies.

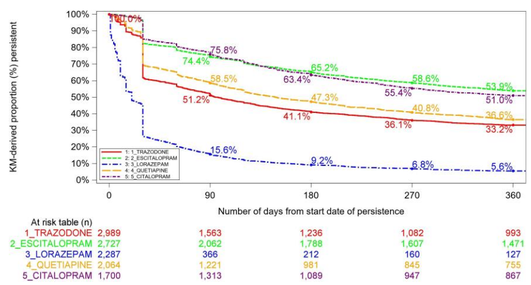
Only the top 10 most common therapies within each line are described.



1L-4L: first to fourth line of therapy

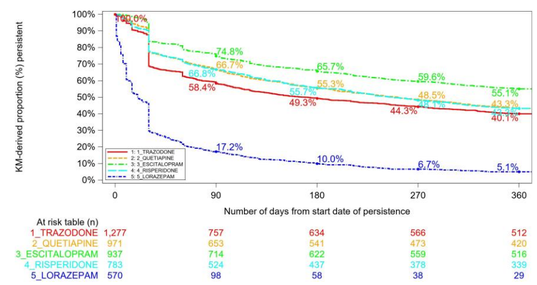
Figure 4. Kaplan-Meier estimates of persistence with the top five 1L – 4L therapies.

A. Persistence on the top five 1L therapies



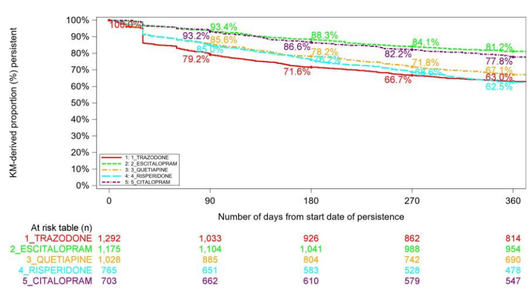
At risk table (n)					
1_TRAZODONE	2,989	1,563	1,236	1,082	993
2_ESCITALOPRAM	2,727	2,062	1,786	1,607	1,471
3_LORAZEPAM	2,287	366	212	160	127
4_QUETIAPINE	2,064	1,221	981	845	755
5_CITALOPRAM	1,700	1,313	1,089	947	867

B. Persistence on the top five 2L therapies



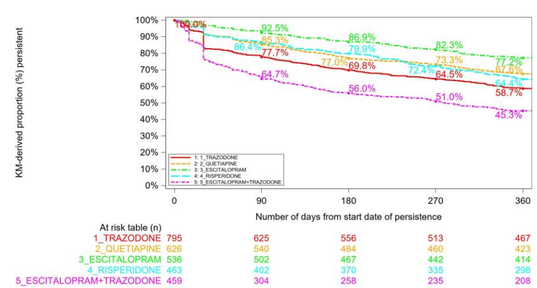
At risk table (n)					
1_TRAZODONE	1,277	757	634	566	512
2_QUETIAPINE	971	653	541	473	420
3_ESCITALOPRAM	937	714	622	559	516
4_RISPERIDONE	783	524	437	378	339
5_LORAZEPAM	570	98	58	38	29

C. Persistence on the top five 3L therapies



At risk table (n)					
1_TRAZODONE	1,292	1,033	926	862	814
2_ESCITALOPRAM	1,175	1,104	1,041	988	954
3_QUETIAPINE	1,028	885	804	742	690
4_RISPERIDONE	785	651	583	528	478
5_CITALOPRAM	703	662	610	579	547

D. Persistence on the top five 4L therapies



At risk table (n)					
1_TRAZODONE	795	625	556	513	467
2_QUETIAPINE	626	540	484	460	423
3_ESCITALOPRAM	536	502	467	442	414
4_RISPERIDONE	463	402	370	335	298
5_ESCITALOPRAM+TRAZODONE	459	304	258	235	208

1L-4L: first to fourth line of therapy