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Research Report

Medications in Patients with Dementia and Behavioral Disturbance

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Abstract.
Background: Behavioral disturbance (BD) is common in dementia patients, with no FDA approved medications for this condition. Little data exists on the real-world medication use in this population.
Objective: To describe real-world medications use in this population.
Methods: A cross-sectional study was conducted using the MarketScan database for outpatient medications and the Cerner database for inpatient medications. The study period was Oct 2015–Jun 2018. Patients with dementia and BD were identified through ICD-10-CM. We examined outpatient medications prescribed during 6-month before or after BD event date, and inpatient medications during inpatient visits, especially on central nervous systems (CNS) drugs including antidementia drugs, antidepressants, antipsychotics, anxiolytics, and anticonvulsants.
Results: A total of 56,544 outpatients and 34,245 patient hospitalizations were assessed separately. Among outpatients, patients filled more medications after a BD event. The use of the five CNS drug classes generally increased after a BD event, and the largest increase was seen in antipsychotics (23% to 33%). Among inpatients, the median number of medications used in each hospitalization was 14. The use of antipsychotics was particularly high (64%), followed by anxiolytics (51%). A list of 60 unique medications were suggested to be the commonly used drugs in dementia patients with BD.
Conclusion: In dementia patients with BD, anti-dementia medications, antidepressants, anticonvulsants, hypnotics and antipsychotics were the most used drug classes. Antidepressants and antipsychotics use were more frequent after a BD event, which suggests a need for safe drugs targeting BD in dementia patients.

Keywords: Behavioral disturbance, Cerner Health Facts, dementia, IBM Marketscan, prescriptions

INTRODUCTION

Dementia is a debilitating, ultimately fatal disease that constitutes a growing challenge to health-care systems due to the aging population. Globally, the number of individuals living with dementia is predicted to increase to 76 million patients by 2030 and 135 million patients by 2050 [1]. Many patients with dementia suffer from behavioral disturbances (BD) such as agitation and psychosis which are often difficult to treat [2]. Studies suggested that more than 90% of dementia patients would experience at least one BD symptom at some point during the course of their illness; and over 60% of dementia patients would experience one or more BD symptom in the past month [3].

When non-pharmacological management is exhausted, pharmacotherapy is often used. There are two challenges in pharmacological management of

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BD in dementia patients. First, there are no FDA approved medications to treat BD in patients with dementia. In clinical practice, various psychotropic medications such as antipsychotics, antidepressants, anxiolytics, and anticonvulsants have been suggested, although none of them is consistently effective [4]. The choice of medication is further complicated by the potential risks of adverse events. Specifically, all antipsychotics carry a black box warning of increased mortality in patients with dementia [5]. The lack of well-established, effective drugs leads to variability in guidelines as well as real-world use, and the real-world treatment practices may be quite different from what guidelines recommend.

The second challenge in the pharmacotherapy of BD in patients with dementia is that patients are usually in advanced age with multiple comorbidities and on multiple prescriptions. The concomitant use of other medications also complicates the pharmacotherapy of BD in patients with dementia because of increased risk of harmful drug-drug interactions (DDIs).

Therefore, data on the rea-world drug use of dementia patients with BD is important to provide necessary background information, which can inform future studies on new drug development (e.g., clinical trial design), DDIs, and quality improvement strategies on optimizing pharmacotherapy in this population.

METHODS

This was a cross-sectional study which examined the real-world medication use in dementia patients with BD using a claims database and an electronic health records (EHR) database.

Data sources

The IBM® MarketScan® Commercial and Medicare Supplemental Database (MarketScan database) is a claims database, which includes inpatient, outpatient, outpatient pharmacy claims and enrollment details from more than 40 million employees, their spouses, and dependents covered by private healthcare insurance with or without Medicare Supplemental. Using this database, we analyzed outpatient prescriptions among dementia patients with BD.

The Cerner Health Facts® database (Cerner database) is a hospital based EHR database that contains pharmacy, lab, clinical and billing data from about 50 million patients across over 600 facilities in the U.S. Using this database, we analyzed inpatient prescriptions among dementia patients with BD.

Study populations

In the MarketScan database, the study population was patients with dementia diagnosis (defined as at least one inpatient or two outpatient diagnosis of dementia) during the study time period of October 2015-December 2018. Because this study aimed to understand real-world medication use among all dementia patients, we did not require an incident dementia diagnosis. The earliest dementia diagnosis date in this study period served as the index date of dementia in this study. The date of first BD event claim (defined as any of the following: agitation, aggression, psychosis, delirium, wandering) on or after index date served as the event date, regardless of whether the BD event was incident or not. The ICD-10-CM codes for dementia and BD are included in the Supplementary Material. As there are three ICD-10-CM dementia codes indicating behavioral disturbance (F01.51, F02.81, and F03.91), the event date and index date could be the same day for some patients. All patients had to have 6-month continuous enrollment before and after the event date, respectively.

In the Cerner database, all hospitalizations with both dementia and BD diagnosis October 2015-December 2018 were included. The analytic unit was encounter, not patient.

Prescription exposure

Prescription exposure was defined as a pharmacy claim with days' supply ≥ 1 day in the MarketScan database, and as an administered medication order with total quantity > 0 in the Cerner database.

Statistical analyses

In the MarketScan database, we described the number of unique active ingredients before and after the BD event date. In the Cerner database, we described the number of unique encounters for each active ingredient. We reported commonly used medications among outpatients (defined as taken by $\geq 5\%$ of the patients) in the MarketScan database and among inpatients (defined as taken by $\geq 10\%$ of the patients) in the Cerner database. We also examined the following five CNS drug classes: antidementia drugs, antidepressants, anxiolytics/hypnotics, antipsychotics, and anticonvulsants.

Finally, we created a summary medication list of commonly used medication in dementia patients with BD by combining results from the Marketscan and Cerner databases, and grouped these medications by drug classes.

All analyses were completed in SAS 9.4 (Cary, NC).

RESULTS

In the MarketScan database, among patients with dementia during the study period October 2015-December 2018, 83,024 patients (35.6%) had at least one BD event on or after dementia diagnosis. The requirement of 6-month continuous enrollment before and after BD decreased the study population to 56,544. About 60% of these patients were female. The mean age was 80.1 years, 90% were 65 years or older, and 44% were 85 years or older. In the Cerner database, a total of 34,245 hospitalizations were included, 55% of them were female. The mean age was 78.5 years, 90% were 65 or older, and 34% were 85 years or older.

Table 1
Medication use among dementia patients with BD

	Marketscan				Cerner	
	6 months before BD		6 months after BD			
No	Generic name	Percent	Generic name	Percent	Generic name	Percent
1	Donepezil	24.8	Donepezil	27.2	Acetaminophen	44.9
2	Metoprolol	20.6	Metoprolol	21.6	Lorazepam	38.3
3	Levothyroxine	20.1	Memantine	21.0	Aspirin	37.3
4	Atorvastatin	18.9	Levothyroxine	20.7	Haloperidol	30.8
5	Memantine	18.4	Atorvastatin	20.2	Quetiapine	28.6
6	Amlodipine	16.3	Quetiapine	18.3	Potassium chloride	28.2
7	Furosemide	15.6	Furosemide	17.6	Pantoprazole	28.0
8	Lisinopril	14.2	Amlodipine	17.5	Metoprolol	26.2
9	Quetiapine	12.4	Lisinopril	14.3	Heparin	25.1
10	Potassium Chloride	11.6	Potassium	13.3	Atorvastatin	23.5
11	Omeprazole	11.5	Sertraline	12.7	Docusate	23.2
12	Sertraline	10.9	Mirtazapine	11.7	Enoxaparin	22.3
13	Simvastatin	10.0	Omeprazole	11.7	Donepezil	22.0
14	Ciprofloxacin	9.3	Trazodone	11.4	Furosemide	20.5
15	Acetaminophen/Hydrocodone	9.2	Lorazepam	10.4	Amlodipine	20.3
16	Tamsulosin	8.6	Tamsulosin	9.9	Levothyroxine	19.1
17	Gabapentin	8.5	Ciprofloxacin	9.7	Ceftriaxone	18.2
18	Trazodone	8.5	Escitalopram	9.5	Ondansetron	17.5
19	Clopidogrel	8.4	Pantoprazole	9.5	Memantine	16.0
20	Escitalopram	8.3	Gabapentin	9.2	Lisinopril	15.7
21	Mirtazapine	8.3	Simvastatin	8.7	Risperidone	14.7
22	Pantoprazole	8.2	Divalproex	8.5	Famotidine	13.5
23	Losartan	8.0	Risperidone	8.4	Hydralazine	13.5
24	Lorazepam	7.9	Acetaminophen/Hydrocodone	8.4	Olanzapine	13.1
25	Metformin	7.7	Clopidogrel	8.3	Morphine	12.9
26	Alprazolam	7.6	Losartan	8.1	Albuterol-ipratropium	12.7
27	Tramadol	7.5	Cephalexin	8.0	Polyethylene glycol 3350	12.6
28	Citalopram	7.4	Citalopram	7.8	Divalproex sodium	12.5
29	Cephalexin	7.2	Tramadol	7.8	Fentanyl	12.0
30	Sulfamethoxazole/Trimethoprim	6.3	Alprazolam	7.6	Trazodone	11.9
31	Carvedilol	6.0	Metformin	7.5	Tamsulosin	11.6
32	Prednisone	5.7	Sulfamethoxazole/Trimethoprim	6.6	Multivitamin	11.4
33	Levofloxacin	5.6	Carvedilol	6.4	Acetaminophen-hydrocodone	10.9
34	Azithromycin	5.6	Levofloxacin	6.3	Magnesium sulfate	10.3
35	Albuterol	5.5	Nystatin	5.9	Cholecalciferol	10.2
36	Risperidone	5.4	Albuterol	5.9		
37	Warfarin	5.3	Prednisone	5.7		
38	Pravastatin	5.3	Polyethylene Glycol 3350	5.6		
39			Azithromycin	5.4		
40			Nitrofurantoin	5.2		
41			Olanzapine	5.0		
42			Carbidopa/Levodopa	5.0		

Among outpatients with dementia, 50,566 (89.4%) had at least one prescription filled during 6 months before or 6 months after the BD event, and they had more unique number of medications after BD event than before BD event (5, 8, 12 versus 6, 9, 13, number of medications before versus after BD event). Among inpatients, the median length of stay was 7 days and the median number of medications used was 14 (Q1 : 9, Q3 : 19).

In outpatients, the top five commonly used medications were donepezil, metoprolol, levothyroxine, atorvastatin, and memantine, and all these medications had slightly higher percentage of usage after the BD date (Table 1). The use of the five CNS drug classes was also generally increased after the BD event (Table 2). The largest increase was seen in antipsychotics, (23% to 33%). There were 21% and 29% outpatients received 3 or more classes of drugs in the five CNS drugs classes before and after BD event, respectively.

In inpatient prescriptions, the top five commonly used prescriptions were acetaminophen, lorazepam, aspirin, haloperidol, and quetiapine (Table 1). The use of antipsychotics was particularly high (64%), followed by anxiolytics/hypnotics (51%) (Table 2). There were 41% inpatients received more than 3 or more classes of drugs in the five CNS drug classes; 31% inpatients received both antipsychotics and antidepressants during hospitalizations.

The medication list of commonly used drugs in both inpatient and outpatient includes 60 unique medications (Table 3). In this list, CNS class had the largest number of unique drugs (23), followed by drugs for metabolic disorders (11), and antibiotics (8).

DISCUSSION

Our study found that dementia patients with BD were exposed to many medications, and the CNS

Table 2
Prevalence (%) of selected CNS drug classes in dementia patients with BD

Drug class	Marketscan		Cerner
	6-month before BD	6-month after BD	
Antidementia drugs	36.9	41.2	31.8
Antidepressants	44.6	50.7	41.9
Antipsychotics	22.7	33.0	63.8
Anxiolytics/hypnotics	19.0	20.8	51.0
Anticonvulsants	22.0	26.7	29.4

*Antidementia drugs include: donepezil, rivastigmine, memantine, galantamine; Antidepressants include: amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxepine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelizine, protriptyline, selegiline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, vilazodone; Antipsychotics include: aripiprazole, asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, mesoridazine, molindone, olanzapine, paliperidone, perphenazine, perphenazine/amitriptyline, pimavanserin, pimozide, prochlorperazine, promazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone; Anxiolytics/Hypnotics include: flurazepam, clonazepam, quazepam, triazolam, lorazepam, alprazolam, temazepam, oxazepam, prazepam, estazolam, flunitrazepam, chlordiazepoxide, clorazepate, diazepam, midazolam, eszopiclone, zaleplon, zolpidem, ramelteon, allobarbital, amobarbital, aprobarbital, alphenal, barbital, brallobarbital, pentobarbital, henobarbital, secobarbital; anticonvulsants include: carbamazepine, ethotoin, fosphenytoin, lacosamide, lamotrigine, oxcarbazepine, rufinamide, phenytoin, gabapentin, phenobarbital, pregabalin, primidone, tiagabine, ethosuximide, clobazam, vigabatrin, levetiracetam, ezogabine, divalproex sodium, felbamate, topiramate, valproate sodium, valproic acid and zonisamide.

Table 3
Commonly used drugs in dementia patients with BD

System	Medications (total number: 60)
CNS (23)	analgesics: acetaminophen, acetaminophen/hydrocodone, aspirin, fentanyl, morphine, tramadol; antidepressants: sertraline, trazodone, citalopram, escitalopram, hydralazine, mirtazapine; antipsychotics: haloperidol, olanzapine, quetiapine, risperidone; anxiolytics/hypnotics: lorazepam, alprazolam; other CNS drugs: carbidopa/levodopa, divalproex, donepezil, gabapentin, memantine
Antibiotics (8)	azithromycin, ceftriaxone, cephalexin, ciprofloxacin, levofloxacin, nitrofurantoin, nystatin, sulfamethoxazole/trimethoprim
Cardiovascular (6)	amlodipine, carvedilol, furosemide, lisinopril, losartan, metoprolol
Gastrointestinal (5)	docusate, famotidine, omeprazole, pantoprazole, polyethylene glycol 3350
Hematological (4)	clopidogrel, enoxaparin, heparin, warfarin
Metabolism (11)	atorvastatin, cholecalciferol, levothyroxine, magnesium sulfate, metformin, multivitamin, ondansetron, potassium chloride, pravastatin, prednisone, simvastatin
Respiratory (2)	albuterol, albuterol-ipratropium
Urological (1)	Tamsulosin

drugs such as antipsychotics and antidepressants were commonly used especially among inpatients, and after a recent BD event. There have been limited studies on the real-world drug use among dementia patients in BD. We found only one study describing medications in dementia patients with BD and reporting the higher frequency of both somatic medications and psychiatry medications, compared to dementia patients without BD [6]. However, that study was focused on disease burden and only certain categories of medications were included. In our study, we evaluated all medications used among dementia patients with BD both in inpatients and outpatients.

Dementia patients with BD may be hospitalized due to various conditions other than dementia or BD. In our study, we found that compared to the outpatients, the inpatients had a higher prevalence of CNS prescriptions including antipsychotics and anxiolytics, thus those inpatients might have more severe form of BD than outpatients. The finding that prescription use in general increased after the BD event, with the largest increase in the antipsychotic class is not unexpected. This increased and common use of antipsychotics, despite the lack of established efficacy and the presence of the black box warning, likely reflects the serious unmet need in managing this difficult condition and the urgency of developing new drugs to treat them safely and effectively. Multiple CNS drugs exposure in this population also suggested that clinicians should be cautious of potential adverse effects of inappropriate prescriptions or DDIs when treating them [7], and our study provided the necessary background data for such investigations and could help optimize pharmacological treatment for patients with BD and dementia.

In new drug development, drug developers need to assess the DDI potential before the product is administered to patients who are likely to take concomitant medications that could interact with the investigational drug. This real-world study findings on the medications used in this population, especially the list of the commonly used medications could help to inform the clinical trial on DDIs, for which the developers need to use a risk-based approach to evaluate the probability of having DDI in clinical practice settings [8].

The prevalence of BD among dementia patients in the MarketScan outpatients was lower than those reported in the literature (that almost all dementia patients will experience BD during the disease course). The cross-sectional study design could be one reason for this finding and the prevalence of BD would be expected to increase with longer follow-up. Also, minor BDs might be managed at home without presenting for medical care (thus not recorded in the claims), and BD events might be under-coded in the claims by the physicians.

The strength of this study included a large sample size in both databases, both of which have been widely used in health service research. One database captured outpatient prescriptions, while the other captured inpatient prescriptions in each hospitalization. Thus, we could obtain a complete picture of pharmacotherapy among dementia patients with BD.

Our study also has limitations. First, we did not consider medication treatment duration or adherence. Second, OTC drugs and alternative medicines were not captured in the databases. Third, we did not require the patients to be incident dementia patients with incident BD for this cross-sectional study. This is because dementia patients could have multiple BD episodes and we aimed to understand medication use among all dementia patients with BD regardless of whether they were incident or non-incident patients. As a result, we cannot determine whether the prescription change was caused by the recent BD event or not. Finally, the diagnosis codes in claims databases may not be accurate, and BD events might be under-coded.

In conclusion, we found that besides anti-dementia medications, antidepressants, anticonvulsants, hypnotics, and antipsychotics were the most used drug classes in patients with BD and AD. The use of antipsychotics was particularly high in outpatients after BD and in inpatients. The findings may help improve pharmacological management in this population and facilitate new drug development for BD in patients with dementia.

CONFLICT OF INTEREST

All the authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, all of whom may own stock and/or hold stock options in the Company.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/ADR-210023.

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