The Effect of Agomelatine in Behavioral and Psychological Symptoms of Dementia

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Objective: Moderate and severe behavioral and psychological symptoms of dementia (BPSD) often need medical treatment to improve symptoms. Agomelatine is a selective melatonergic (MT1/MT2) agonist that has normalizing effects on disturbed circadian rhythms and disrupted sleep-wake cycles. Its activity of 5HT-2C receptor antagonism is associated with lessening depression and anxiety and increasing slow-wave sleep. Based on past clinical records and current findings it suggests that agomelatine can improve BPSD for patients. This retrospective cohort study was designed to compare the BPSD before and after using agomelatine.

Methods: Records of dementia cases who had ever received agomelatine treatment for BPSD in a general hospital setting during the past 2.5 years were identified and reviewed. Scores from before and after 3 months of treatment with agomelatine were collected for Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression (CGI) to compare and analyze the difference of psychological and behavioral symptoms pre- and post-agomelatine used.

Results: Records of 144 cases of dementia with BPSD who had ever used agomelatine from January 2015 to June 2017 were collected. All of the 112 cases had BPRS and CGI scores, of which 75 cases had additional NPI scores. Among these 112 cases, the BPRS and CGI scores were significantly improved in all types of dementia. NPI scores indicated that the use of agomelatine alleviated obvious symptoms and decreased overall distress, especially in the depression/poor mood, anxiety, and sleep/night behavior.

Conclusion: It is consistent with an effective result of agomelatine in improving BPSD.

KEY WORDS: Dementia; Behavioral and psychological symptoms; Treatment; Depression; Sleep/night behavior.

INTRODUCTION

Patients with dementia often have behavioral and psychological symptoms (behavioral and psychological symptoms of dementia, BPSD), which include disturbed perception, thought content, mood, behavior and sleep. The common symptoms include agitation, aggression, psychosis, depression, apathy, repetitive questioning, psychosis, sleep problems, wandering, and a variety of socially inappropriate behaviors [1]. A previous study showed that around 80% of demented patients exhibit at least one BPSD from the onset of cognitive symptoms; the most frequent disturbances were apathy (36%), depression (32%), and agitation/aggression (30%) [2]. Similarly, the Cache County study found that the five-year BPSD prevalence (of at least one symptom) was 97%, with the most common symptoms being apathy, depression, and anxiety [3]. Studies in Taiwan showed that the prevalence of BPSD was from...
87.6 to 92%. The prevalence of paranoid/delusional ideation is from 39.5 to 62%, hallucination from 28.6 to 30.7%, activity disturbances 67.2%, aggressiveness from 31.2 to 34.1%, diurnal rhythm disturbances from 38.0 to 43.8%, affective disturbance 35.8%, depression 44.2%, appetite and eating abnormalities 29.7%, and anxiety/phobias 58.4% [4,5]. These BPSD cause more disability for patients as well as increased distress and lower quality of life for both patients and their caregivers. They are associated with misuse of medication, increased and long term hospitalization opportunities, early nursing home admission, higher mortality rates, and increased in health care costs [6-10]. Improving BPSD can reduce the deterioration of the quality of life for patients and their caregivers.

Depression is a common BPSD in different forms of dementia. In Alzheimer’s disease (AD), the most common type of dementia, depression ranges from 25 to 75% in recent studies [11-14]. In the most recent studies, depression in AD is around 37%. In the second most common type of dementia, vascular dementia (VaD), depression occurs in around 48.3% of cases. In the third most common dementia, dementia with Lewy bodies (DLB), depression occurs in around 49% of the cases, and in the fourth common frontotemporal dementia, the prevalence of depression is 36% [15,16]. Diagnosing depression is difficult in dementia because patients have difficulty expressing and recognizing their own emotional condition, and are unstable with commonly used depression scales. Furthermore, the variability of depression prevalence is likely due to the multitude of instruments used for diagnosis, including the Diagnostic and Statistical Manual of Mental Disorders (DSM), Neuropsychiatric Inventory Depression subscale (NPI-D), and Geriatric Depression scale [13,17].

The other common symptoms, agitation and psychosis, are correlated with depression in dementia [18]. One recent study shows high prevalence of agitation in AD and the structure of agitation consists of more aggressive (such as hitting, kicking, grabbing onto people, scratching, spitting, tearing things, throwing things, making physical sexual advances, cursing or verbal aggression screaming, making verbal sexual advances etc.) and physically non-aggressive (such as pacing, aimless wandering, intentional falling, inappropriate dressing and/or disrobing, inappropriate eating or drinking, handling things, hiding things, hoarding, repetitious mannerisms, restlessness etc.) behavior than in mild cognitive impairment cases [19,20]. Depressive symptoms in mild cognitive impairment appear to be predictors for a progression to AD [21]. Hence, it is possible that treating depression in dementia can improve the other severe BPSD symptoms, and reduce cognitive function deterioration.

Although the first line of treatment of BPSD is non-pharmacological intervention, the studies in United States, Germany, Australia and the Netherlands show that 40—70% of BPSD are moderate-to-severe, and require psychotrophic medications [22-24]. Cholinesterase inhibitors and memantine have been used for improving cognitive dysfunction of dementia, but their use for BPSD is controversial, as studies do not report a unanimous improvement of BPSD [25]. Of all agents currently used for BPSD, atypical antipsychotics have the strongest evidence base and are the main ones, although their benefits are moderate at best [25-27]. A lot of adverse events associated with atypical agents, such as the risk of anticholinergic effects, delirium, hyperprolactinemia, postural hypotension, prolonged QT intervals, sexual dysfunction, extrapyramidal symptoms, weight gain, diabetes, metabolic syndrome, cognitive worsening, and even seizure or somnolence were reported [25,28,29]. Kales et al. [30] and US Food and Drug Administration reports suggested that these drugs may increase the mortality rate of patients with dementia.

Antidepressants have been thought to improve the agitation and psychotic symptoms of dementia, especially trazodone, sertraline and citalopram [31,32-34]. The systematic review of literature in 2011 indicates that antidepressants not only show efficacy in treating patients with BPSD but are also well tolerated [34]. Patient with AD did benefit from these drugs but not DLB. A randomized controlled study showed that most patients with behavioral disturbances or psychosis associated with DLB tolerate citalopram poorly and do not seem to benefit from this medication [35]. The other recent review on 2017 concluded that the evidence for efficacy of antidepressants in BPSD is mixed and limited [36]. The antidepressants are most helpful for treating agitation and less for depression, apathy, anxiety, or psychosis in dementia [36]. In addition, harms that are attributable to the use of antidepressants, which are common and in some cases, serious [36,37]. The adverse side-effects of antidepressants are an important consideration, such as nausea and vomiting, headaches, sleep changes, diarrhea, tremor, falls, sexual dysfunction, hyponatremia owing to the syndrome.
of inappropriate antidiuretic hormone secretion, gastrointestinal bleeding and QT interval prolongation [25,35-38]. The randomized control study of citalopram on AD showed that cognitive worsening and QT interval prolongation observed in the citalopram group raise concern about the 30 mg/day dose [38]. Banerjee et al. [39] suggested that because of the absence of benefit compared with placebo and the increased risk of adverse events, the present practice of use of these antidepressants (sertraline and mirtazapine), with usual care, for first-line treatment of depression in AD should be reconsidered.

Agomelatine, an atypical antidepressant, is a selective melatonergic (MT1/MT2) agonist, which was approved by the European Drug Administration in 2009 and Taiwan in 2011. It also stimulates the activity of melatonin MT1 and MT2 receptors and inhibits the activity of serotonin 5HT-2C receptor subtypes [40,41]. The activity of MT1/MT2 has a normalizing effect on disturbed circadian rhythms and disrupted sleep–wake cycles. The activity of 5HT-2C receptor antagonism is associated with lessening depression and anxiety and also increasing slow-wave sleep [40,42]. Depression in AD is thought to be associated with the reduction of circulating melatonin in the central nervous system [43]. Hardeland [43] showed that through the regulation of melatonin receptor agonist, the cholinergic system could be protected, and the locomotor activity could be improved. Agomelatine is also an antioxidant and exhibits anti-inflammatory activity. It also restores stress-affected hippocampal neuronal activity and promotes adult hippocampal neurogenesis and neuroplasticity [44-46]. Furthermore, studies have shown that this drug improves Parkinson’s disease with depression while reducing the extrapyramidal symptoms [47].

In light of the above, we presumed that agomelatine might be able to improve the BPSD of dementia. Agomelatine, as well as other antidepressants, is now prescribed not only for severe depression, but also for mild depression, anxiety, alcohol-dependent associated sleep disturbance, fibromyalgia, and migraine [48,49]. Agomelatine had been proved excellent efficiency in treating severe major depression in seniors with no serious adverse effects [50]. In our clinical practice, for those cases that the depression-related symptoms were not improved or that the side effects from using other various antidepressants were unacceptable, we prescribed agomelatine in off-label for BPSD. The aim of this study is to evaluate the efficacy of agomelatine in BPSD by retrospective analysis of patients before and after agomelatine treatment.

METHODS

There are a significant number of dementia patients in our neurological and psychiatric clinics. Most of these outpatients undergo a series of detailed medical history inquiries and records, neurological psychiatric symptoms tests, blood tests, and imaging examinations to establish the type of dementia. They also have regular neuropsychological test records and BPRS assessments. Therefore, the retrospective study was used to detect patients with dementia who used or were using agomelatine. Their medical records and various examination records were analyzed to explore the various physical and mental changes they experienced from before to after agomelatine treatment to determine its efficacy. The data collection and analysis are described below. It had been approved by the Institute Review Board of National Cheng Kung University Hospital for publication (protocol number B-ER-106-004 and date of approval January 20, 2018).

Inclusive Cases

We reviewed those chart records from January 2015 to June 2017 and computer screened the data base of patients older than 55 years old and less than 90 years old dementia cases who were ever treated with agomelatine. According to the diagnosed records of those ever taking agomelatine, the dementia types were separated into the categories AD, DLB, VaD, mixed type dementia, and other types of dementia. The diagnosis was confirmed by a series of history-taking, physical, neurologic and mental status examinations, laboratory examinations, and brain image studies. All the dementia participants were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) [51]. They all also had ever received a series of neuropsychological screen tests, Clinical Dementia Rating (CDR) scale, Mini-Mental State Examination, or Cognitive Abilities Screening Instrument (2.0) to corroborate the diagnosis of cognitive dysfunction [52,53].

Brief Psychiatric Rating Scale, Clinical Global Impression, and Neuropsychiatric Inventory Scoring Records

Using the medical records, the Brief Psychiatric Rating
Scale (BPRS), Neuropsychiatric Inventory (NPI), or Clinical Global Impression (CGI) data for those patients who were treated with agomelatine for 3 months were collected pre and post treatment. BPRS has been published since 1962 and is the oldest and most widely used psychiatric rating scale [54]. It was initially developed to assess symptom domains in schizophrenia, but has also been used in a number of different settings, including AD clinical trials [55]. CGI is a simple evaluation tool for evaluating symptom severity and improving status after treatment [56]. BPRS and CGI are widely used clinically, and approved assessment tools. NPI is a commonly used tool for BPSD records in patients with dementia, and the BPSD changes are assessed by the primary caregivers, often at less than five minutes. NPI shows good test-retest reliability and convergent validity [57]. It contains 12 questions, evaluates severity (0 – 36 points) and distress (0 – 60 points) for caregivers.

Medicines History Collection

The type of antidepressant used before agomelatine, the reason of changing to agomelatine, reasons for discontinuing the agomelatine (if discontinued), the adju nctive medicines pre- and post-agomelatine treatment. The side effects pre- and post-agomelatine treatment are also collected.

Statistical Analysis

The paired-\( t \) test, Wilcoxon Signed Ranks test and linear mixed-effect model analysis were used to compare the NPI, BPRS, CGI pre-and post-agomelatine using. All statistical analyses were performed by Statistical Package for Social Science 20.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

According to the historical data, there are totally 443 cases available having diagnosis of dementia from January 2015 to June 2017, of which 380 cases (85.8%) had BPSD, 296 cases (77.9% among the latter) had depression-like symptoms and received various antidepressants. Records showed 144 cases of dementia with BPSD had ever used agomelatine. There are 112 of them took agomelatine for 3 months or longer and had records of BPRS and CGI scores, and 75 of the 112 cases also had NPI score records, pre- and post-agomelatine use. The other 32 cases had less than 3 months of treatment or lacked BPRS or NPI records. The reasons for this were (1) 3 cases with BPSD improvement after agomelatine use who transferred to local clinic near their house; (2) 3 cases lack of NPI or BPRS, in them, 2 cases showed BPSD but using duration less than 3 months and 1 using over 3 months but neither NPI nor BPRS and CGI record; (3) 8 cases withdrew from clinic for unknown reasons, but records in 4 cases showed improvement; (4) 4 cases rejected agomelatine after initial use, among them one became violent once at midnight, one increased falling down risk at night, and two rejected to state the reason; (5) 6 cases changed to other medicines because of side effects, such as headache, dizziness or over sedation; (6) 5 cases changed to other medicines because of no improvement of BPSD; (7) 3 cases stopped back to clinic because two cases died, and one developed pneumonia. In the cases of death or pneumonia, they had multiple and complicated physical conditions, also had multiple medicine use. Agomelatine was excluded to be a factor related to the pneumonia or death. Overall, 13 of these 32 cases had improvement recorded after using agomelatine.

Among those 112 cases that using agomelatine more than three months and having BPRS and CGI records, there are 70 females and 42 males, with an average age of 80 years old (as shown in Table 1). The dementia types of these 112 cases include 36 AD, 25 DLB, 23 VaD, 20 mixed type dementia, and 8 other type dementia. Mixed type dementia refers to two or more types of dementia simultaneously, such as AD+VaD, ESRD combined with AD or intracranial hemorrhage or infarctions. Other type dementia includes 3 cases of normal pressure hydrocephalus, 2 cases of dementia due to intracranial hemorrhage, 1 progressive supranuclear palsy, 1 Parkinson’s disease with dementia, and 1 alcohol related dementia. The CDR scores in these 112 cases can be categorized as the following: CDR 0.5, \( n = 5 \), CDR 1.0, \( n = 45 \), CDR 2.0, \( n = 40 \), CDR 3.0 \( n = 18 \) cases, and the other 4 cases having no CDR score, during the usage of agomelatine. No case with obvious cognitive decline were recorded during the 3 months when using agomelatine.

Reasons for shifting from other various antidepressants, such as sertraline, citalopram, escitalopram, paroxetine, venlafaxine, duloxetine, mirtazepine, bupropion, imipramine, doxene or trazodone, to agomelatine were either
Table 1. Demographic data and neuropsychological tests results

| Variable                | AD  | DLB | Mixed type dementia* | VaD  | Othersb | Total |
|-------------------------|-----|-----|-----------------------|------|---------|-------|
| NPI                     |     |     |                       |      |         |       |
| Male                    | 4   | 5   | 3                     | 10   | 4       | 26    |
| Male mean age (yr)      | 83.0| 76.8| 82.3                  | 82.4 | 74.8    | 80.2  |
| Female                  | 21  | 16  | 7                     | 5    | 0       | 4     |
| Female mean age (yr)    | 80.6| 80.5| 80.9                  | 84.4 | -       | 81.0  |
| Total                   | 25  | 21  | 10                    | 15   | 4       | 75    |
| Mean age (yr)           | 81.0| 79.6| 81.3                  | 83.1 | 74.8    | 80.7  |
| BPRS/CGI                |     |     |                       |      |         |       |
| Male                    | 7   | 9   | 7                     | 13   | 6       | 42    |
| Male mean age (yr)      | 83.6| 74.5| 81.1                  | 80.8 | 75.3    | 79.3  |
| Female                  | 29  | 16  | 13                    | 10   | 2       | 70    |
| Female mean age (yr)    | 80.9| 80.5| 81.3                  | 84.4 | 73.0    | 81.2  |
| Total                   | 36  | 25  | 20                    | 23   | 8       | 112   |
| Mean age (yr)           | 81.4| 78.4| 81.3                  | 82.4 | 74.8    | 80.4  |

Values are presented as number.
AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; VaD, vascular dementia; NPI, Neuropsychiatric Inventory; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression.

*Mixed type dementia: include those two or more causes of dementia. Others: include 3 normal pressure hydrocephalus, 2 dementia due to intracranial hemorrhage, 1 progressive supranuclear palsy, 1 Parkinson’s disease with dementia, and 1 alcohol related dementia.

that the depression-related symptoms were not improved or that the side effects from using these antidepressants were unacceptable. These side effects include psychomotor slowing, drowsiness or insomnia, dizziness, fatigue, weakness, increasing extrapyramidal symptoms, loss of appetite, constipation, bruising or increased skin itching. After shifting to agomelatine in these 112 cases, neither liver dysfunction-related symptoms nor other side effects were recorded.

Comparison of CGI tests show that for all types of dementia treatment with agomelatine significantly improved mental symptoms ($p < 0.001$) (Table 2).

Confounding factors were examined: 1) Use of antipsychotic agents: 51 cases either did not use any antipsychotic agents or did not change the dose from pre- to post-agomelatine treatment; 30 cases stopped or reduced the dosage; 17 cases increased the dose; and 14 cases could not have pre- to post-agomelatine comparisons due to changing the agent type or unknown name of antipsychotic drug. 2) Use of hypnotic—sedative agents: 49 cases either did not use any or did not change the dose from pre- to post-agomelatine treatment; 29 cases stopped or reduced the dosage; 18 cases increased the dosage; 16 cases could not have pre- to post-agomelatine comparisons due to using a different type of drug or to unknown drugs’ name. 3) Use of trazodone: 25 cases were treated with trazodone (average dose 50 mg per night) as adjuvant therapy for sleep disturbance, and 3 stopped trazodone after agomelatine treatment. After controlling for age, sex, sedative/hypnotic agent, antipsychotics and trazodone with linear mixed-effect model analysis, the BPRS scores after using agomelatine for three months or more were significantly lower than the pre-agomelatine scores ($p = 0.007$) (Table 3). Agomelatine improved the BPSD of dementia. Thus, a total of 86.8% (125 in 144) cases present the improvement of BPSD by agomelatine. At least 8 cases (5.6%) ever had side effects which include headache, dizziness, over sedation, increasing falling down or violence risk.

Each of the sub-items of BPRS except for the disorientation one, when analyzed for total dementia cases, shows significant improvement after agomelatine treatment. In each individual dementia type, except the other dementia classification, the following items show the most improvement: ‘somatic concern’, ‘anxiety’, ’guilty feeling’, ‘tension’, ‘depressive mood’, ‘hostility’, ‘suspicousness’, ‘hallucinatory behavior’, ‘uncooperativeness’, and ‘unusual thought content’. Even for the other dementia classification, the scores are all larger for pre-agomelatine use than for post-agomelatine use, though the small sample size makes it difficult to reach significance.

The other 4 items—emotional withdrawal, mannerism and posturing, grandiosity and disorientation show no significant difference when looking at separated dementia
| Diagnosis                  | Total (n = 112) | AD (n = 36) | DLB (n = 25) |
|----------------------------|----------------|-------------|--------------|
|                            | v1            | v2          | WSRT         | p value  | v1            | v2          | WSRT         | p value  |
| BPRS total                 | 31.5 ± 10.9   | 21.3 ± 7.3  | -8.96       | < 0.001   | 29.4 ± 12.2  | 19.9 ± 8.2  | -5.09       | < 0.001   |
|                            | 1.8 ± 1.5     | 1.3 ± 1.1   | -5.27       | < 0.001   | 1.8 ± 1.5    | 1.1 ± 1.1   | -3.37       | < 0.001   |
|                            | 2.6 ± 1.4     | 1.6 ± 1.1   | -6.83       | < 0.001   | 2.6 ± 1.3    | 1.7 ± 0.9   | -4.12       | < 0.001   |
|                            | 1.0 ± 1.2     | 0.8 ± 0.8   | -3.33       | 0.001     | 1.0 ± 1.3    | 0.8 ± 1.0   | -1.90       | 0.058     |
|                            | 2.0 ± 1.6     | 1.7 ± 1.4   | -3.03       | 0.002     | 1.6 ± 1.6    | 1.4 ± 1.2   | -1.89       | 0.059     |
|                            | 0.8 ± 1.0     | 0.4 ± 0.5   | -5.51       | < 0.001   | 1.0 ± 1.0    | 0.5 ± 0.6   | -3.21       | < 0.001   |
|                            | 2.8 ± 1.4     | 2.1 ± 0.9   | -5.88       | < 0.001   | 2.6 ± 1.2    | 2.0 ± 0.7   | -3.11       | 0.002     |
|                            | 0.4 ± 1.2     | 0.2 ± 0.7   | -2.47       | 0.014     | 0.4 ± 1.3    | 0.3 ± 0.9   | -1.86       | 0.063     |
|                            | 0.1 ± 0.3     | 0.0 ± 0.2   | -2.24       | 0.025     | 0.1 ± 0.2    | 0.0 ± 0.0   | -1.41       | 0.157     |
|                            | 2.1 ± 0.9     | 0.9 ± 0.7   | -8.79       | < 0.001   | 2.0 ± 1.0    | 0.8 ± 0.8   | -4.94       | < 0.001   |
|                            | 1.6 ± 1.9     | 0.5 ± 0.9   | -6.36       | < 0.001   | 1.6 ± 1.8    | 0.4 ± 0.7   | -3.59       | < 0.001   |
|                            | 1.8 ± 1.9     | 0.7 ± 1.1   | -6.16       | < 0.001   | 1.8 ± 2.0    | 0.9 ± 1.3   | -3.15       | 0.002     |
|                            | 1.8 ± 2.0     | 0.6 ± 1.0   | -6.18       | < 0.001   | 1.4 ± 2.0    | 0.4 ± 0.8   | -3.06       | 0.002     |
|                            | 2.5 ± 1.2     | 2.3 ± 1.1   | -3.45       | < 0.001   | 1.9 ± 1.1    | 1.9 ± 1.1   | -0.58       | 0.564     |
|                            | 1.1 ± 1.2     | 0.7 ± 0.6   | -3.77       | < 0.001   | 1.0 ± 1.1    | 0.7 ± 0.6   | -2.06       | 0.039     |
|                            | 2.3 ± 2.0     | 1.2 ± 1.4   | -6.17       | < 0.001   | 2.2 ± 2.1    | 1.1 ± 1.5   | -3.07       | 0.002     |
|                            | 2.1 ± 1.2     | 1.9 ± 1.1   | -3.87       | < 0.001   | 1.8 ± 1.2    | 1.7 ± 1.1   | -1.34       | 0.180     |
|                            | 0.7 ± 1.1     | 0.5 ± 0.8   | -3.79       | < 0.001   | 0.8 ± 1.0    | 0.5 ± 0.7   | -2.53       | 0.011     |
|                            | 4.0 ± 1.2     | 3.9 ± 1.2   | -1.41       | 0.157     | 3.8 ± 1.2    | 3.8 ± 1.1   | -1.00       | 0.317     |
|                            | 4.9 ± 1.0     | 2.4 ± 0.5   | -9.14       | < 0.001   | 4.7 ± 1.1    | 2.4 ± 0.5   | -5.14       | < 0.001   |
| CGI                        | 4.9 ± 1.0     | 2.4 ± 0.5   | -9.14       | < 0.001   | 4.7 ± 1.1    | 2.4 ± 0.5   | -5.14       | < 0.001   |
Table 2. Continued

| Diagnosis                        | Mixed type dementia (n = 20) |                  |                  |                  |                  |                  |                  |                  |                  |                  |                  |
|----------------------------------|-----------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                  |                             | v1               | v2               | WSRT             | p value          | v1               | v2               | WSRT             | p value          | v1               | v2               | WSRT             | p value          |
| BPRS total                       |                             | 31.5 ± 7.6       | 22.8 ± 5.7       | −3.83            | < 0.001          | 32.4 ± 9.5       | 22.2 ± 7.3       | −4.20            | < 0.001          | 24.4 ± 6.9       | 17.3 ± 4.7       | −2.37            | 0.018            |
| Somatic concern                  |                             | 1.1 ± 1.3        | 0.9 ± 1.2        | −1.63            | 0.102            | 2.6 ± 1.4        | 1.9 ± 1.1        | −2.68            | 0.007            | 1.3 ± 1.3        | 1.3 ± 1.3        | 0.00             | > 0.999          |
| Anxiety                          |                             | 2.2 ± 1.4        | 1.5 ± 1.0        | −2.41            | 0.016            | 2.9 ± 1.2        | 1.9 ± 1.3        | −3.45            | 0.001            | 1.5 ± 1.4        | 1.3 ± 1.3        | −1.00            | 0.317            |
| Emotional withdrawal             |                             | 0.9 ± 1.2        | 0.6 ± 0.6        | −1.34            | 0.180            | 0.8 ± 0.5        | 0.7 ± 0.4        | −1.00            | 0.317            | 1.4 ± 1.6        | 0.8 ± 0.5        | −1.34            | 0.180            |
| Conceptual disorganization       |                             | 2.0 ± 1.3        | 1.9 ± 1.3        | −1.00            | 0.317            | 2.0 ± 1.7        | 1.9 ± 1.6        | −0.75            | 0.453            | 2.8 ± 2.0        | 2.0 ± 1.8        | −0.16            | 0.109            |
| Guilt feelings                   |                             | 0.6 ± 1.0        | 0.2 ± 0.4        | −2.33            | 0.020            | 0.6 ± 0.6        | 0.3 ± 0.4        | −2.65            | 0.008            | 0.8 ± 0.9        | 0.4 ± 0.5        | −0.13            | 0.083            |
| Tension                          |                             | 2.1 ± 1.4        | 1.8 ± 0.8        | −1.29            | 0.197            | 3.1 ± 1.4        | 2.2 ± 1.0        | −2.96            | 0.003            | 2.3 ± 0.7        | 1.8 ± 0.5        | −0.13            | 0.102            |
| Mannerisms and posturing         |                             | 0.7 ± 1.8        | 0.2 ± 0.5        | −1.60            | 0.109            | 0.3 ± 1.1        | 0.2 ± 0.8        | −1.34            | 0.180            | 0.0 ± 0.0        | 0.0 ± 0.0        | 0.00             | > 0.999          |
| Grandiosity                      |                             | 0.1 ± 0.4        | 0.1 ± 0.4        | 0.00             | > 0.999          | 0.0 ± 0.0        | 0.0 ± 0.0        | 0.00             | > 0.999          | 0.1 ± 0.4        | 0.0 ± 0.0        | 0.00             | −1.00            | 0.317            |
| Depressive mood                  |                             | 2.4 ± 1.0        | 1.3 ± 0.6        | −3.38            | 0.001            | 2.2 ± 0.7        | 0.9 ± 0.8        | −4.28            | < 0.001          | 1.9 ± 0.8        | 0.8 ± 0.5        | −2.46            | 0.014            |
| Hostility                        |                             | 1.6 ± 1.8        | 1.1 ± 1.2        | −2.33            | 0.020            | 2.0 ± 2.1        | 0.6 ± 1.0        | −3.20            | 0.001            | 0.1 ± 0.4        | 0.0 ± 0.0        | −1.00            | 0.317            |
| Suspiciousness                   |                             | 1.4 ± 2.0        | 0.5 ± 1.1        | −2.39            | 0.017            | 2.2 ± 2.0        | 0.7 ± 1.1        | −3.33            | 0.001            | 0.8 ± 1.5        | 0.5 ± 1.4        | −0.10            | 0.317            |
| Hallucinatory behavior           |                             | 1.9 ± 2.0        | 1.0 ± 1.3        | −2.64            | 0.008            | 1.5 ± 2.0        | 0.3 ± 0.8        | −2.51            | 0.012            | 1.6 ± 1.8        | 0.3 ± 0.7        | −1.84            | 0.066            |
| Motor retardation                |                             | 2.7 ± 1.3        | 2.4 ± 0.8        | −1.60            | 0.109            | 2.5 ± 1.0        | 2.3 ± 1.0        | −1.63            | 0.102            | 3.0 ± 1.4        | 2.4 ± 1.3        | −1.63            | 0.102            |
| Uncooperativeness                |                             | 1.2 ± 1.5        | 0.7 ± 0.5        | −1.60            | 0.109            | 1.1 ± 1.1        | 0.8 ± 0.5        | −1.89            | 0.059            | 0.5 ± 0.5        | 0.5 ± 0.8        | 0.00             | > 0.999          |
| Unusual thought content          |                             | 3.5 ± 1.7        | 1.7 ± 1.5        | −3.33            | 0.001            | 2.1 ± 2.1        | 1.3 ± 1.5        | −2.72            | 0.007            | 0.3 ± 0.7        | 0.1 ± 0.4        | −0.20            | 0.317            |
| Blunted affect                   |                             | 2.2 ± 1.0        | 2.2 ± 1.0        | −1.00            | 0.317            | 2.0 ± 1.2        | 1.9 ± 1.3        | −1.73            | 0.083            | 2.6 ± 1.7        | 1.9 ± 1.2        | −2.12            | 0.034            |
| Excitement                       |                             | 0.7 ± 0.7        | 0.7 ± 0.7        | 0.00             | > 0.999          | 0.9 ± 1.6        | 0.5 ± 1.1        | −2.25            | 0.024            | 0.1 ± 0.4        | 0.1 ± 0.4        | 0.00             | > 0.999          |
| Disorientation                   |                             | 4.4 ± 0.7        | 4.4 ± 0.7        | −1.00            | 0.317            | 3.7 ± 1.1        | 3.7 ± 1.0        | −1.00            | 0.317            | 3.5 ± 1.7        | 3.4 ± 1.6        | −1.00            | 0.317            |
| CGI                              |                             | 5.2 ± 1.0        | 2.5 ± 0.5        | −3.99            | < 0.001          | 5.1 ± 0.8        | 2.3 ± 0.5        | −4.25            | < 0.001          | 4.5 ± 0.8        | 2.1 ± 0.4        | −2.56            | 0.011            |

Values are presented as mean ± standard deviation.
v1, pre-agomelatine using; v2, post agomelatine using; WSRT, Wilcoxon Signed Ranks test; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression.

Mixed type dementia: include those two or more causes of dementia. Others: include 3 normal pressure hydrocephalus, 2 dementia due to intracranial hemorrhage, 1 progressive supranuclear palsy, 1 Parkinson’s disease with dementia, and 1 alcohol related dementia.
groups, though they do show statistically significant reduction after agomelatine use for total dementia cases.

NPI records caregivers’ rating the severity of symptoms and distress of the patient’s experience. The analysis of the NPI records for the 75 cases who were on agomelatine for three or more months shows that use of agomelatine markedly reduced most symptoms and overall distress (p < 0.001), especially in the items of delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, disinhibition, irritability,lability, motor disturbance, sleep/nighttime behavior after agomelatine use since these symptoms were rarely noted for these patients before using agomelatine. But in using the BPRS scores, more cases with hallucinatory behaviors in the patients with VaD dementia were found. And the significant improvement with agomelatine use was impressive.

For the ‘agitation/aggression’, ‘disinhibition’ and ‘irritability/lability’ items of NPI, as well as for the ‘hostile’ item of BPRS, most show the remarkable improvement. However, effects of agomelatine on these items could not be measured for the other type dementia category, since the cases involved show no aggression-related behavior pretreatment, and no difference was noted.

For the item of emotional withdrawal in BPRS and the item ‘apathy/indifference’ in NPI there was no significant difference between pre- and post-agomelatine use in each dementia group, but significant improvement when all dementia cases were combined.

The item of motor disturbance, with high severity and distress scores in the DLB and VaD types of dementia, significantly improved for them after agomelatine use. All types of dementia, except the other type category, show significant improvement for the item ‘nighttime behavior after agomelatine use. Severity for the item ‘appetite/eating’ showed significant improvement in the AD group, but not in any other types of dementia.

**DISCUSSION**

The neuropsychiatric symptoms in dementia cases are heterogeneous and largely unpredictable, affecting emotional experience, thought content, perception, and motor function [58]. They can be understood as ineffective attempts of the patient to cope with environmental or physiological stress factors. Pharmacological approaches are considered only after non-pharmacological strategies failed to improve BPSD [59]. However, most drugs are not approved for BPSD and their use is therefore off-label. Thus, in considering treatment effects, it is important to understand underlying causal mechanisms and to develope

| Effect                        | Estimate | Standard Error | p value |
|-------------------------------|----------|----------------|---------|
| Interceptor                   | -16.6675 | 10.0507        | 0.102   |
| Agomelatine                   | -4.4635  | 1.6123         | 0.007   |
| Age                           | 0.1200   | 0.1030         | 0.248   |
| Sex                           | -2.7594  | 1.6537         | 0.100   |
| Dementia type                 |          |                |         |
| AD                            | -0.7398  | 3.1782         | 0.817   |
| DLB                           | -4.1352  | 3.3305         | 0.218   |
| VaD                           | -2.0335  | 3.4743         | 0.560   |
| Mixed                         | -1.7149  | 3.4463         | 0.620   |
| Other (reference)             |          |                |         |
| Add other antidepressants     | 2.4402   | 2.2089         | 0.273   |
| Reduce other antidepressants  | -1.4567  | 5.0480         | 0.774   |
| Add sleeping medication       | 2.2571   | 2.2279         | 0.314   |
| Reduce sleeping medication    | -3.3782  | 1.6300         | 0.031   |
| Add antipsychotic agent       | -2.1728  | 2.3652         | 0.361   |
| Reduce antipsychotic agent    | -4.7867  | 1.7654         | 0.008   |

Table 3. The estimated and adjusted effect of agomelatine on BPRS after controlled for age, sex, dementia types, and the use of psychotropic medication.

AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; VaD, vascular dementia; BPRS, Brief Psychiatric Rating Scale.
| Diagnosis                  | Severity | Distress | AD (n = 25) | Distress |
|---------------------------|----------|----------|-------------|----------|
|                           | v1       | v2       | p value     | v1       | v2       | p value     |
| Delusions                 | 1.5 ± 1  | 0.7 ± 0.8| −5.43 < 0.001| 2.1 ± 1.9| 0.9 ± 1.3| −5.50 < 0.001|
| Hallucinations            | 1.2 ± 1.3| 0.5 ± 0.7| −4.57 < 0.001| 1.5 ± 1.8| 0.6 ± 1.1| −4.24 < 0.001|
| Agitation/Aggression      | 1.5 ± 1.2| 0.8 ± 1.0| −4.93 < 0.001| 2.3 ± 1.9| 1.1 ± 1.4| −5.02 < 0.001|
| Depression/Dysphoria      | 1.8 ± 1.1| 0.7 ± 0.7| −6.19 < 0.001| 2.4 ± 1.6| 0.9 ± 1.1| −6.22 < 0.001|
| Anxiety                   | 1.7 ± 1.1| 0.9 ± 0.8| −4.72 < 0.001| 2.3 ± 1.8| 1.1 ± 1.2| −5.01 < 0.001|
| Elation/Euphoria          | 0.2 ± 0.5| 0.1 ± 0.3| −1.20 < 0.230| 0.2 ± 0.7| 0.1 ± 0.2| −1.79 < 0.074|
| Apathy/Indifference       | 1.1 ± 1.2| 0.8 ± 1.0| −2.44 < 0.015| 1.4 ± 1.7| 1.0 ± 1.4| −2.96 < 0.003|
| Disinhibition             | 1.2 ± 1.3| 0.7 ± 0.9| −3.68 < 0.001| 1.7 ± 1.9| 1.0 ± 1.4| −3.57 < 0.001|
| Irritability/Lability     | 1.8 ± 1.2| 0.9 ± 1.0| −5.60 < 0.001| 2.5 ± 1.7| 1.3 ± 1.5| −5.44 < 0.001|
| Motor disturbance         | 1.2 ± 1.2| 0.7 ± 1.0| −3.64 < 0.001| 1.5 ± 1.8| 0.9 ± 1.3| −4.22 < 0.001|
| Nighttime behaviors       | 2.1 ± 1.1| 1.0 ± 0.9| −5.61 < 0.001| 2.9 ± 1.8| 1.2 ± 1.3| −5.78 < 0.001|
| Appetite/Eating           | 1.0 ± 1.1| 0.6 ± 0.9| −2.93 < 0.003| 1.4 ± 1.7| 0.9 ± 1.5| −2.64 < 0.008|
| Total                     | 16.1 ± 7.0| 8.4 ± 5.7| −7.14 < 0.001| 22.2 ± 11.2| 10.9 ± 9.5| −6.93 < 0.001|
|                           |          |          |              | 12.7 ± 6.3| 7.1 ± 5.2| −4.24 < 0.001|

Table 4. NPI differences between pre- and post agomelatine use in each group.
### Table 4. Continued

| Diagnosis                  | VaD (n = 15) |                      |                      | Others (n = 4) |                      |                      |
|----------------------------|--------------|----------------------|----------------------|----------------|----------------------|----------------------|
|                            | Severity     | Distress             |                      | Severity       | Distress             |                      |
|                            | v1           | v2                   | v1                   | v2             | WSRT                 | p value              |
| Delusions                  |              |                      |                      |                |                      |                      |
|                           | 1.7 ± 1.3    | 0.9 ± 1.0            | −2.81, 0.005         | 2.5 ± 2.1      | 1.1 ± 1.4            | −2.59, 0.010         |
| Hallucinations             |              |                      |                      |                |                      |                      |
|                           | 1.1 ± 1.3    | 0.5 ± 0.8            | −1.56, 0.119         | 1.3 ± 1.7      | 0.6 ± 1.1            | −1.55, 0.121         |
| Agitation/Aggression       |              |                      |                      |                |                      |                      |
|                           | 2.0 ± 1.0    | 0.9 ± 1.2            | −2.68, 0.007         | 2.8 ± 1.7      | 1.2 ± 1.8            | −2.33, 0.020         |
| Depression/Dysphoria       |              |                      |                      |                |                      |                      |
|                           | 1.7 ± 1.0    | 0.7 ± 0.9            | −2.74, 0.006         | 2.5 ± 1.7      | 0.9 ± 1.3            | −2.83, 0.005         |
| Anxiety                    |              |                      |                      |                |                      |                      |
|                           | 2.1 ± 1.1    | 0.9 ± 0.9            | −2.71, 0.007         | 2.9 ± 1.7      | 1.1 ± 1.2            | −3.05, 0.002         |
| Elation/Euphoria           |              |                      |                      |                |                      |                      |
|                           | 0.6 ± 1.1    | 0.1 ± 0.4            | −1.63, 0.102         | 0.8 ± 1.5      | 0.1 ± 0.4            | −1.79, 0.074         |
| Apathy/Indifference        |              |                      |                      |                |                      |                      |
|                           | 1.1 ± 1.1    | 1.0 ± 1.1            | −0.52, 0.603         | 1.9 ± 1.8      | 1.4 ± 1.7            | −1.41, 0.157         |
| Disinhibition              |              |                      |                      |                |                      |                      |
|                           | 1.3 ± 1.2    | 0.9 ± 1.0            | −1.28, 0.201         | 1.9 ± 1.9      | 1.3 ± 1.6            | −1.24, 0.217         |
| Irritability/Lability      |              |                      |                      |                |                      |                      |
|                           | 2.1 ± 0.8    | 1.2 ± 1.1            | −2.50, 0.013         | 3.1 ± 1.3      | 1.7 ± 1.7            | −2.46, 0.014         |
| Motor disturbance          |              |                      |                      |                |                      |                      |
|                           | 1.6 ± 1.2    | 1.0 ± 1.1            | −2.25, 0.024         | 2.0 ± 1.9      | 1.5 ± 1.9            | −2.27, 0.023         |
| Nighttime behaviors        |              |                      |                      |                |                      |                      |
|                           | 2.1 ± 1.1    | 1.0 ± 0.8            | −2.95, 0.003         | 3.3 ± 1.8      | 1.1 ± 1.2            | −2.91, 0.004         |
| Appetite/Eating            |              |                      |                      |                |                      |                      |
|                           | 1.0 ± 1.2    | 0.7 ± 1.0            | −1.52, 0.129         | 1.5 ± 1.9      | 0.9 ± 1.8            | −1.91, 0.056         |
| Total                      |              |                      |                      |                |                      |                      |
|                           | 18.4 ± 4.6   | 9.9 ± 6.8            | −3.18, 0.001         | 26.3 ± 9.0     | 13.0 ± 10.2          | −3.23, 0.001         |

Values are presented as mean ± standard deviation.

v1, pre-agomelatine using; v2, post agomelatine using; WSRT, Wilcoxon Signed Ranks test; NPI, Neuropsychiatric Inventory.

Mixed type dementia: include those two or more causes of dementia. Others: include 1 normal pressure hydrocephalus, 1 dementia due to intracranial hemorrhage, 1 Parkinson’s disease with dementia, and 1 alcohol related dementia.
op etiological-based therapeutic interventions. Yet, it is hard to appropriately recognize and describe the psychopathology and accurately distinguish between similar symptoms (e.g., depression vs. apathy), and there is a lack of proper definitions and consensus criteria for their diagnosis [58]. Nonetheless, some of neurotransmitter changes in brains of dementia cases have been implicated in the etiology of BPSD [60]. Defining these neuroanatomical and neurochemical correlates of BPSD has been an area of active research with a hope that clarification of the underlying neurobiology will lead to more effective treatments [58]. These neurotransmitters include serotonin, dopamine, glutamate, noradrenaline and cholinergic agents. Brain-region-specific monoaminergic neurotransmitters and their metabolites alterations, such as dopamine, serotonin, and noradrenaline, are related to specific neuropsychiatric symptoms: psychosis, agitation, aggression, and affective disturbances [61]. Cholinergic imbalance also has been proposed to be associated with psychotic symptoms, agitation and aggression in AD [62]. Furthermore, melatonin and melatonin receptor agonists can be effective in treating circadian sleep disorders in dementia [63,64]. One animal study suggested that melatonin could be used as a potential candidate drug to improve the neuropsychiatric behaviors in AD via modulating the expression of the proteins (i.e., GSTP1 and CPLX1) involved in anxiety and depression behaviors [65]. Agomelatine has the activities of selective melatonergic (MT1/MT2) agonist and 5HT-2C receptor antagonism. This may explain why the results of BPRS and NPI showed that agomelatine can improve the BPSD, especially depression, anxiety, delusions, hallucinations, and irritability.

The statistical results show the consistency of the item of emotional withdrawal in BPRS and apathy/indifference in NPI with no significant difference between pre- and post-agomelatine use in each dementia group, but improvement when combining all dementia cases. This discrepant result might be due to small samples in each group. A previous review showed that agomelatine has positive effects for apathy but other antidepressants did not [66]. The effect of 5-HT2C receptor antagonism in agomelatine is thought to leads to an increase in prefrontal dopaminergic and noradrenergic tone, and decreases apathy for fronto-temporal dementia [67]. Thus, agomelatine might improve the emotional withdrawal or apathy as well.

Since presentations of grandiosity, mannerisms and posturing in the BPSD symptoms of these dementia patients were rare before agomelatine use in this study, it is predictable that there would be no difference between pre- and post-agomelatine use. In the item of NPI ‘disinhibition’, only the severity (severity) and the degree of distress (distress) in DLB, and the degree of distress assessed by caregivers in AD showed significant improvement. In general, DLB patients tend to have a higher rate of disinhibition [68]. Recent studies have shown that disinhibition is more frequent in patients with visual hallucinations [69,70]. In AD, inhibitory performance not only significantly correlated with hallucinations but also mediated the relationship between depression and hallucinations [70]. Disinhibition, not surprisingly, improved along with the improvement in visual hallucination and depression in this study.

There were no obvious side effects to the use of agomelatine, except for a few headaches, drowsiness, and dizziness. It shows that agomelatine is a safe drug for geriatric dementia applications. However, elderly patients with dementia often have other multiple physical conditions as well. Hence, the determination of dose still must comply with the principle of start low go slow. This study shows that agomelatine use has some impact on parkinsonism. Other reports have shown this as well [47].

Limitations

There is no paper published that explores the agomelatine effect on BPSD yet, except less than one third part of the results of the current research were previously published in abstract form at the American Association for Geriatric Psychiatry Annual Meeting held in Atlanta, Georgia in 2019. A number of limitations of this study must be considered. (1) Because this study is a single group with retrospective, pre- and post-test design, some confounding factors and periodic monitoring cannot be properly controlled and recorded. For example, non-pharmacological strategies before and during agomelatine use were not controlled for. (2) The study is relatively small sample size to examine the possible effects of the pharmacological intervention in BPSD. Participants were included from a general hospital that may not generalize to other settings. (3) The measurement instruments were not ideal: Though BPRS has been used for screening BPSD of dementia, some of its items are thought to be irrelevant,
unspecific or confounded by cognition [71]. Thus, NPI, the Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer’s Disease or, the Behavioral Pathology in Alzheimer’s Disease Scale are recommended for measuring neuropsychiatric symptoms in studies of patients with dementia [72].

From this study, agomelatine is a safe drug for geriatric dementia applications. There is an association between improvement of certain neuropsychiatric symptoms and use of agomelatine.

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### Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

Study design: Carol Sheei-Meei Wang, Chia-Hung Tang, Pei-Fang Chien. Data acquisition: Carol Sheei-Meei Wang, Chia-Hung Tang, Pei-Fang Chien. Data analysis and interpretation: Carol Sheei-Meei Wang, Pai-Lien Chen. Supervision: Kuo-Sheng Cheng, Ming-Chyi Pai. Writing—original draft: Carol Sheei-Meei Wang. Writing—review & editing: Pai-Lien Chen. Carol Sheei-Meei Wang and Ming-Chyi Pai had primary responsibility for the final content. All authors read and approved the final manuscript.

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