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Drug Therapy for Behavioral and Psychological Symptoms of Dementia

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Abstract: Dementia, which can be induced by diverse factors, is a clinical syndrome characterized by the decline of cognitive function. Behavioral and psychological symptoms of dementia (BPSD) include depression, agitation, and aggression. Dementia causes a heavy burden on patients and their caregivers. Patients with BPSD should be assessed comprehensively by practitioners and offered appropriate non-pharmacologic and pharmacologic therapy. Non-pharmacologic therapy has been recommended as the basal treatment for BPSD; however, pharmacologic therapy is required under many situations. Medications, including antipsychotic agents, antidepressants, sedative and hypnotic agents, mood stabilizers, cholinesterase inhibitors, and amantadine, are extensively used in clinical practice. We have reviewed the progression of pharmacologic therapy for BPSD.

Keywords: Alzheimer's disease, antipsychotic, behavioral and psychological symptoms of dementia, dementia, drug, psychiatric symptoms.

1. INTRODUCTION

Dementia is a syndrome caused by pathologic changes in the brain. The main clinical manifestation of dementia is a decline in cognitive function. There were 44 million patients with dementia worldwide in 2013, and the population is estimated to increase to 135 million in 2050 [1]. The causes of dementia include Alzheimer's disease (AD), vascular dementia, and others, such as Parkinson's disease dementia, frontotemporal dementia, and Lewy Body dementia. AD is the most common etiology for dementia. AD was first reported by Alzheimer in 1906 [2]. The patient in his report was a female who had multiple behavioral and psychological symptoms, including delusions, sexual hallucinations, screaming episodes, and aggression. Nearly all patients with dementia may develop behavioral and psychological symptoms of dementia (BPSD) with progression of the disease. The symptoms and frequency of BPSD may vary, but include hallucinations, delusions, agitation, depression, apathy, aggression, and sleep disorders [3-11]. The different types of dementia have characteristic manifestations. For example, visual hallucinations are prominent in Lewy body dementia, while disinhibition and aggression are more common in frontotemporal dementia [12-14]. It has been reported that > 80% of patients with impaired cognitive function display psychological and behavioral abnormalities. Specifically, the incidence of delusions, hallucinations, depression, anxiety, apathy, agitation, and aggression is 3%–54%, 1%–39%, 8%–74%, 7%–69%, 17%–84%, 48%–82%, and 11%–44%, respectively [15]. A 5-year follow-up of demented patients by Steinberg *et al*. [16] concluded that 97% of patients experienced at least one psychological and behavioral symptom. Indeed, the symptom with the highest 5-year period prevalence was depression (77%), followed by apathy (71%) and anxiety (62%) [16]. BPSD seriously influences the quality of life in demented patients and is a major reason for increased hospitalization and mortality. BPSD also increases the economic burden for families and society. The treatment of BPSD remains a challenge for practitioners [17-22]. The current treatment of BPSD mainly focuses on delusions, hallucinations, agitation, and aggression.

2. DRUG THERAPY

Treatment of BPSD depends on the potential risk of BPSD to patients and their caregivers. Some guidelines suggest that patients with dementia should first be fully assessed. The factors which may induce abnormal mentation and behavior, such as pain, delirium, environmental factors, and interpersonal factors, should be excluded [23-26]. The treatment of BPSD includes non-pharmacologic and pharmacologic therapies. This review summarizes the progression of BPSD treatment. Notably, non-pharmacologic therapy is recommended as first-line treatment of BPSD and pharmacologic therapy can be used when non-pharmacologic therapy fails [27, 28].

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The drugs for BPSD mainly include antipsychotic agents, antidepressants, sedative and hypnotic agents, mood stabilizers, cholinesterase inhibitors, and amantadine.

2.1 Antipsychotics

2.1.1. Typical Antipsychotics

A systematic study, which included two meta-analyses and two randomized controlled trials, indicated that the efficacy of typical antipsychotics in controlling BPSD is limited, whereas the side effects are common [24, 29-32]. Haloperidol can effectively control the aggression of patients with dementia; however, due to side effects, haloperidol is not recommended to treat other psychological and behavioral symptoms [29]. Moreover, the utility of haloperidol should be personalized and the side effects should be closely monitored.

2.1.2. Atypical Antipsychotics

Recently, the application of atypical antipsychotics has increased significantly because the drugs cause less adverse reactions compared with typical antipsychotics. Atypical antipsychotics have been widely used in treating dementia accompanied by BPSD. The efficacy of atypical antipsychotics in improving psychological and behavioral symptoms has been confirmed by many studies [24, 33-36, 38, 39]. In the meantime, the side effects gain more attention.

Based on a meta-analysis, both aripiprazole and risperidone have been shown to improve BPSD [33]. Olanzapine was not proven to have this favorable effect and the efficacy of quetiapine could not be assessed [33]. In addition, all four drugs can cause adverse reactions, such as somnolence, urinary tract infections, and urinary incontinence. However, another meta-analysis suggested that olanzapine has efficacy in improving agitation and aggression [34]. Risperidone and olanzapine both effectively improve the agitation of patients with dementia, and risperidone was shown to improve psychotic symptoms [35]. A systematic review summarized six randomized controlled trials (RCTs) involving atypical antipsychotics, and concluded that olanzapine and risperidone have statistically significant efficacy in treating BPSD, although the effect was moderate [24]. Another systematic review published in 2015 analyzed the efficacy of atypical antipsychotics [36]; six RCTs were included in this study. The results suggested that compared with placebo, atypical antipsychotics significantly reduced the total NPI score of the patients (SMD: –0.21 , 95% CI: –0.29 to –0.12). A subgroup analysis indicated that olanzapine and aripiprazole reduced the NPI score significantly (SMD: 0.18 , 95% CI: –0.31 to –0.04 and SMD: –0.20 , 95% CI: –0.35 to –0.05, respectively). With respect to the effect of quetiapine, the conclusions were not consistent [37]. A placebo-controlled study in 2007 reported that 200 mg/d of quetiapine significantly improved agitation symptoms; however, at a dose of 100 mg/d, the efficacy was not significantly different from placebo [38]. In a placebo-controlled study, aripiprazole showed efficacy in controlling BPSD, particularly psychotic and agitation symptoms [39]. There are no related controlled studies that have investigated the efficacy of clozapine in treating BPSD.

2.1.3. Side effects of Antipsychotic Drugs

The adverse reactions associated with typical antipsychotics mainly include cerebral-vascular accidents, anticholinergic effects, Parkinson syndrome, and tardive dyskinesia.

Many studies have confirmed the efficacy of risperidone in treating BPSD [24 , 33 , 35]. Compared with olanzapine, risperidone has fewer side effects, including somnolence, weight gain, abnormal metabolism, and anticholinergic effects [40]. Risperidone is also associated with some adverse reactions, including extrapyramidal reactions, hyperprolactinemia, osteoporosis, orthostatic hypotension, and an increased risk of falls [33, 40]. Risperidone may also increase the risk of cerebrovascular accidents [33].

In spite of the efficacy in improving BPSD, the side effects of olanzapine, including excessive sedation, weight gain, metabolic syndrome, orthostatic hypotension, extrapyramidal symptoms, and anticholinergic effects, are significant [35].

Quetiapine has relatively mild side effects, including slight extrapyramidal symptoms and anticholinergic effects, as well as metabolic disorders [41]. However, the main concerns with quetiapine are excessive sedation and orthostatic hypotension.

Ripiprazole has a favorable tolerability profile. Serious adverse reactions associated with aripiprazole are rare. The most common reported adverse reaction associated with aripiprazole is somnolence [39]. The application of aripiprazole in the treatment of dementia does not increase the risk of cardiovascular or cerebrovascular accidents, as well as weight gain [39]. Clinically significant changes in the ECG have not been observed in patients treated with aripiprazole [42].

The risks of extrapyramidal symptoms and tardive dyskinesia induced by clozapine are relatively low [41]. The adverse reactions associated with clozapine mainly include severe neutropenia, abnormal metabolism, decreased threshold of seizures, weight gain, and orthostatic hypotension.

Among the adverse reactions induced by antipsychotic drugs, cerebrovascular accidents should receive more attention. A meta-analysis showed that the incidence of strokes in the antipsychotic drug group was 1.9% compared to 0.9% in the placebo group; the OR was 2.13 and the 95% CI was 1.20–3.75 [34]. There is a study that has suggested typical antipsychotics might increase the risk of stroke (RR=1.69, 95% CI: 1.55–1.84) [43]. The risk for stroke associated with atypical antipsychotics in patients with dementia is even higher (RR=2.32, 95% CI: 1.73–3.10) [43].

In April 2005, the FDA published a public health recommendation. When atypical antipsychotics are used in elderly patients with dementia, the increased risk for stroke must be considered. A study conducted in Canada suggested that the utility of antipsychotics increases the mortality in patients with dementia after 30, 60, 120, and 180 days of the treatment. The risk of death associated with typical antipsychotics is higher than atypical antipsychotics [44].

In 2012, a large-sample retrospective cohort study included 33,604 patients with dementia who were > 65 years of age and were treated with antipsychotics [45]. The results showed that there was a difference in the mortality of patients treated with different antipsychotics [45]. The haloperidol group had the highest mortality (RR: 1.54; 95% CI: 1.38–1.73), followed by the risperidone (RR: 1 [reference group]) and olanzapine groups (RR: 0.99, 95% CI: 0.89–1.10). The quetiapine group had the lowest mortality (RR: 0.73, 95% CI: 0.67–0.80). In addition, there was no significant difference in mortality between the valproic acid and risperidone groups (RR: 0.91, 95% CI: 0.78–1.06).

Practitioners should adopt a personalized therapeutic regimen. The side effects of antipsychotic drugs should be closely monitored and the balance between potential risk and benefit should also be carefully assessed.

2.2. Antidepressants

Tricyclic antidepressants have been shown to have little effect in treating symptoms of depression in patients with dementia; the drugs also have many side effects.

The efficacy of SSRIs in treating symptoms of depression in patients with dementia has been extensively studied. A systematic review suggested that SSRIs have mild efficacy in improving symptoms; however, due to the small sample size (four studies were included), and only two studies involving SSRIs, the conclusions were not definitive [46, 47]. A 2012 meta-analysis [48] concluded that there is no adequate evidence to verify that SSRIs have definite efficacy in treating symptoms of depression in patients with dementia [48–53]. These studies had heterogeneity in diagnostic standards, choice of SSRI drugs, and judgment of outcomes, which might have contributed to indefinite conclusions about the efficacy of SSRIs in treating symptoms of depression. In addition, two RCTs involving sertraline indicated that the drug was not significantly different from placebo in reducing the NPI total score of patients with dementia [36].

In a multicenter, randomized, double-blind, placebo-controlled trial, mirtazapine did not show efficacy in improving the symptoms of depression in patients with dementia. In contrast, placebo had fewer side effects compared to mirtazapine [53].

Despite having no significant efficacy in controlling depression or reducing the total score of NPI in patients with dementia, antidepressants may be effective in treating agitation and psychotic symptoms in these patients.

SSRIs, including sertraline and citalopram, can reduce the agitation and psychotic symptoms of patients with dementia compared to placebo [54]. A 2014 RCT reported that compared with placebo, citalopram significantly reduced the symptoms of agitation in AD patients and decreased the burden of caregivers [55]. A study compared the difference between citalopram and risperidone in treating agitation and psychotic symptoms of patients with dementia; the result suggested that both in controlling agitation symptoms and reducing psychotic symptoms, citalopram and risperidone had no significant difference [56]. The authors suggested additional studies are warranted to validate the efficacy of citalopram, as well as other SSRIs in treating agitation and psychotic symptoms of patients with dementia [56].

Trazodone is effective in controlling the agitation symptoms in patients with dementia [46]. A placebo-controlled trial showed that trazodone can improve abnormal behaviors in AD patients.

Sixteen AD patients with agitation symptoms were followed in a prospective study [57]. The Cohen–Mansfield Agitation Inventory short form score and Clinical Global Impression Severity scale after 12 weeks of treatment with mirtazapine were significantly decreased compared with pre-treatment values ($P < 0.001$) [57]. The authors suggested that the efficacy of mirtazapine in controlling agitation symptoms of patients with dementia could not be determined due to a lack of controlled studies which evaluate the efficacy of mirtazapine in treating the symptoms.

2.3. Sedative and Hypnotic Drugs

Benzodiazepines can control the acute restlessness and agitation in dementia. A systematic review summarized five RCTs, in which one study compared diazepam and thioridazine, one study compared oxazepam, haloperidol, and diphenhydramine, one study compared alprazolam and lorazepam, one study compared lorazepam and haloperidol, and one study compared lorazepam and olanzapine [58]. Four of the RCTs suggested that there were no significant differences in controlling behavioral and psychological disturbances associated with dementia between sedative and hypnotic drugs, including oxazepam, lorazepam, and alprazolam, and antipsychotic drugs, including thioridazine, haloperidol, and olanzapine [58]. The tolerability of these drugs had no significant difference either; however, it is worth noting that in two RCTs, approximately one-third of patients quit the trials. For the sake of adverse reactions associated with sedative and hypnotic drugs, for example, excessive sedation, dizziness, reduction in cognitive function, falls, drug dependence, and withdrawal reactions, benzodiazepines are not recommended as a conventional therapy for BPSD [59].

2.4. Mood Stabilizers

A 2001 clinical trial evaluated the efficacy, tolerability, and safety of a 6-week treatment regimen with divalproex sodium for symptoms of agitation in patients with dementia [60]. The drug might have efficacy in treating agitation, and the tolerability and safety were acceptable. The conclusion needs further studies for validation [60]. As a continuation of the study above, a 2003 clinical trial confirmed the efficacy of divalproex sodium in improving symptoms of agitation in patients with dementia [61]; however, a 2005 multi-center clinical trial yielded an inconsistent conclusion because treatment with divalproex sodium (800 mg/d for 6 weeks) did not show efficacy in improving agitation in dementia [62]. A systematic review in 2009, based on previous studies, concluded that compared with placebo, valproates do not effectively improve symptoms of agitation in patients with dementia. In contrast, valproates increase the incidence of adverse reactions (for example, falls, gastrointestinal

reactions, infections, and sedation) [63], thus valproates are not recommended for the routine control of BPSD.

Another systematic review [64] also suggested that the efficacy of valproates in controlling BPSD was limited [60, 64-66]. Moreover, the review analyzed multiple drugs, such as carbamazepine, gabapentin, lamotrigine, and topiramate [64]. Carbamazepine was shown to improve BPSD, but the drug has many side effects, including sedation, hyponatremia, cardiac toxicity, and allergy. Carbamazepine is also a hepatic enzyme inducer and increases the risk of drug-drug interactions [64, 67-69]. In spite of the efficacy and safety of gabapentin in treating BPSD, some case reports and clinical trials have suggested that validation of the effects of gabapentin is needed *via* double-blind, placebo-controlled studies. Few studies exist concerning lamotrigine; however, lamotrigine increases the risk of Steven–Johnson syndrome, thus lamotrigine is not recommended to control BPSD. Theoretically, oxcarbazepine can act as an alternative to carbamazepine, but there is a lack of related clinical trials regarding the drug [64]. Currently, with the exception of carbamazepine, the evidence of other mood stabilizers in controlling BPSD is limited. The efficacy and safety of mood stabilizers warrant further studies.

2.5. Cholinesterase Inhibitors and Amantadine

Cholinesterase inhibitors, including donepezil, rivastigmine, and galanthamine, have weak therapeutic effects on BPSD. A meta-analysis indicated that compared with placebo, cholinesterase inhibitors improve the NPI score (total score: 0–120; improvement: 1.72; 95% CI: 0.87–2.57) and there were no significant differences in efficacy among various cholinesterase inhibitors [70]. The slight improvement in the NPI score might have no clinical significance. A 12-week clinical trial in 2007 found that compared with placebo, donepezil failed to improve the agitation symptoms in patients with dementia [71]. A randomized, double-blind, clinical trial which included 565 AD patients followed up for 2 years showed that there were no significant differences in improving BPSD in AD patients among three groups (5 mg/d of donepezil, 10 mg/d of donepezil, and placebo) [72].

A study indicated that cholinesterase inhibitors can improve the BPSD evaluation scale in patients with Parkinson's disease dementia (SMD: –0.20; 95% CI : –0.36 to –0.04, P = 0.01), but the efficacy in improving BPSD associated with Lewy body dementia is inconclusive [73]. Furthermore, patients treated with cholinesterase inhibitors have a risk to aggravate Parkinson-like symptoms (particularly tremors), even though the UPDRS score didn't worsen.

A 2012 randomized, double-blind clinical trial evaluated the therapeutic efficacy of amantadine in treating agitation in AD patients [74]. The results suggested that amantadine did not improve the agitation symptoms in these patients [74]. After a 6-week treatment, amantadine reduced the Cohen–Mansfield Agitation Inventory (CMAI) score (SMD: –3.0; 95% CI: –8.3 to 2.2, P = 0.26), but lacked statistical significance. Amantadine significantly improved the NPI score of AD patients (at 6 weeks, SMD: –6.9; 95% CI: –12.2 to –1.6, P = 0.012 ; at 12 weeks, SMD: –9.6; 95% CI: –15.0 to –4.3, P = 0.0005).

Cholinesterase inhibitors may induce adverse reactions, including nausea, vomiting, and diarrhea. Amantadine is associated with headache, dizziness, and confusion. Even though the side effects are not serious, the side effects of amantadine should be considered in clinical practice [74-77].

3. CONCLUSION

In conclusion, BPSD is a group of symptoms accompanied with dementia. In some cases, the condition becomes a more important problem than the decrease in cognitive function. Because the condition brings a heavy mental or economic burden for patients, caregivers, families, and society, the symptoms should be actively treated and controlled. The first step is to make a full and thorough evaluation for patients with dementia and identify those factors which may induce or aggravate the symptoms. Non-pharmacologic therapy is first-line treatment. If non-pharmacologic therapy fails, pharmacologic therapy can be considered; however, these drugs generally have more or less side effects, especially for elderly people, thus the ratio of benefit-to-risk should be carefully assessed before treatment. Furthermore, regular follow-up and evaluation should be performed after the treatment, so that the therapeutic regimens can be adjusted according to the status of patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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