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Review

New hope for Behavioural and Psychological Symptoms in Dementia (BPSD): A Narrative review of clinical studies conducted in the symptomatic treatments for agitation and psychosis episodes in Alzheimer's disease/dementia.

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Background: *The psychomotor agitation of the BPSD is one of the common issues in aged care facilities, leading to the poor functional and medical consequences. Psychotropic interventions are the preferable choice of treatment. But which medication should be the prescribers first preference? This review aims to compare pharmacological interventions for psychomotor agitation, judging them according to their effectuality and justifiability profiles. This is to be achieved by retrieving information from RCTs and systematic reviews.* ***Objectives:*** *This review evaluates evidence from RCTs, systematic reviews, and meta-analyses of BPSD patients who had taken agitation treatments. Assessing the efficacy of antidepressants and antipsychotic treatments when compared to each other for the purpose of improving agitation outcomes.* ***Methods:*** *This narrative review includes RCTs and retrospective studies that were comparing one or more active ingredient medications with another or with a placebo, along with systematic reviews comparing antidepressants with antipsychotics such as quetiapine, olanzapine, and risperidone. Studies extracted by searching accessing databases, such as PubMed, OVID, and Cochrane with restrictions of date from 2000 to 2021 and English language.* ***Quality of evidence****: The quality of systematic reviews was judged against AMSTAR score, and RCTs were judged according to CONSORT checklist for RCT protocols.* ***Conclusion:*** *There are still few studies of serotonin targeting treatment of agitation in BPSD. The SSRIs such as citalopram were associated with a reduction in symptoms of agitation, and lower risk of adverse effects compared to antipsychotics. This review also illustrates brexpiprazole as a target of multimodal neurotransmitters such as dopamine, serotonin, and norepinephrine; and dextromethorphan, OR dextromethorphan associated with bupropion or quinidine as a blockade of NMDA receptors. The outcome of this review suggests that further studies involving more dementia/Alzheimer's participants should be conducted. Future studies are required also to assess the long-term safety and efficacy of SSRI, brexpiprazole, dextromethorphan treatments for agitation in BPSD.*

Keywords: BPSD, Alzheimer's dementia, agitation, psychosis, SSRIs, antipsychotics, brexpiprazole, dextromethorphan.

1. Introduction

Behavioural and psychological symptoms of dementia (BPSD) are non-cognitive neuropsychiatric symptoms and represent a common heterogeneous group of psychopathological signs that occur in older people with cognitive impairment. It affects up to 90% of all individuals with dementia over the course of their illness (Magierski et al., 2020). BPSD encompasses potentially disruptive behaviours associated with significant functional and clinical impairment, such as aberrant motor behaviours, apathy, sleep disturbance, agitation, anxiety, depression, irritability, psychosis, delusions, hallucinations, and appetite changes. These symptoms have been recognised as risk factors of dementia, especially when co-occurring with psychotic and effective symptoms (Carrarini et al., 2021). Consequently, BPSD has the potential to negatively impact quality of life, illness, treatments, deterioration of family and professional relationships, and caregiver burdens (Seitz et al., 2011). Therefore, the treatment of BPSD must be individualised according to four factors: (1) adequate pain management, (2) managing somatic disease(s), (3) optimise non-pharmacological plan and interventions, (4) pharmacotherapy (Carrarini et al., 2021). Treatment of agitation in Behavioural and Psychological Symptoms of Dementia (BPSD) can improve quality of life and reduce patient suffering. Usually, agitation treatment can be initiated by non-pharmacological intervention such as behavioral management, environmental modification, sensory interventions, and social interaction groups (Seitz et al., 2011). However, in many dementia cases, behavioral interventions alone cannot control agitation episodes. Therefore, pharmacological treatment will be added (Lee et al., 2015). The primary goal of pharmacological intervention is to rapidly calm the agitated patient. The treatment needs to be used in conjunction with verbal de-escalating and environmental

modification techniques. Where possible, the selection of medication needs to be given firstly as a monotherapy, with rapid onset of action a desirable feature (Lee at al., 2015). The recent psychiatry evidence determined four classifications of underlying causes of agitation in dementia: (1) psychiatric disorders, (2) undifferentiated agitation, (3) medical condition, (4) substance intoxication/withdrawal symptoms (Schnelli et al., 2021). The preferred pharmacological treatment option will be determined by the underlying causes of agitation. The common classifications for psychiatric disorders are anxiety disorders, affective disorders, personality, and adaptive disorder. These conditions can be treated by benzodiazepines, while psychotic disorders such as schizophrenia, bipolar disorders, mental retardation, and autism spectrum disorders can be managed by antipsychotics (Schnelli et al., 2021). The common conditions of undifferentiated agitation are cognitive impairment and confessional syndrome, these conditions are usually treated using intramuscular or oral atypical antipsychotics, while agitation due to substance intoxication/withdrawal symptoms is treated by intramuscular benzodiazepines (Schnelli et al., 2021). Of concern, the options of treatment in classes of agitation are only antipsychotics and benzodiazepines. Despite of the efficacy of these treatments, they can however, have serious adverse effects, especially in vulnerable patients such as older people with dementia. Moreover, there is evidence suggesting these medications are involved in the progression of cognitive decline and contribute to the development of metabolic and cardiovascular diseases (Schnelli et al., 2021). For these reasons, clinicians are still working to identify novel therapeutics for dementia, focusing on symptomatic treatments for agitation and psychosis. One of the alternative classes of medication to antipsychotics are SSRI medications (Stahl, 2019). Several RCT studies have occurred in Europe and the United States, to examine the efficacy and the safety of one of these SSRIs, citalopram, for dementia associated agitation (Pollock et al., 2007). These trials proposed that citalopram is likely a safer alternative to antipsychotics and provides greater benefits with clinically significant reduction of agitation, with fewer side effects. SSRIs have been linked with mild cognitive and cardiac adverse effects compared to antipsychotics and benzodiazepines (Schnelli et al., 2021). Porsteinsson et al. compared citalopram with placebo in RCT-double blinded of participants. The results of this study stated that citalopram is as effective as antipsychotics for managing agitation in dementia, and more effective than antipsychotics when looking for improvement at the mADCS-CGIC scale for agitation (Porsteinsson et al., 2014). The dose guideline for citalopram in US-FDA 2011 indicated a maximum 20mg daily for older people due to concerns around prolongation of QT interval and cardiac events (Vieta et al., 2017). However, the same updated guideline in 2016 incorporated some amendments to their protocol and stated that citalopram did not demonstrate an elevated risk of cardiovascular problems, and that the cases of cardiac events with greater dose of citalopram versus lower dose are non-significant after review (Vieta et al., 2017). On the other hand, Munro et al. 2012 examined the effects of SSRIs in patients with depression and agitation of Alzheimer's dementia, the results indicated that there are no significant changes in MMSE score after treatment and did not establish a difference from placebo (Vieta et al., 2017). In general, there is as yet no study comparing the efficacy and safety between antipsychotics and SSRIs in managing agitation of dementia in Australia. There is also a paucity of valid evidence, examining SSRIs for the treatment of agitation in dementia. The research which is available identifies a need for further studies to examine the efficacy and the safety of antipsychotics and SSRIs in aged care residents involving more participants in different facilities.

Pharmacological treatments for agitation associated with dementia

Agitation is a state of emotional stress that the patient is unable to self-regulate consisting of; disinhibition, excessive psychomotor activities, irritability, and aggressiveness. These symptoms are quite common in older residents with dementia. The aetiology of agitation is based on the impairment of top-down cortical control of impulsive behaviours, and also irregular bottom-to—up drive from limbic regions of brain, or agitation either caused or exacerbated by psychosis (Stahl et al., 2019). First line treatment needs to be addressing the potential causative agent of agitation. Therefore, before commencing treatment, it could be beneficial to apply the Cohen-Mansfield Agitation Inventory Scale (29-item). This scale can be used to assess both aggressive and non-aggressive physical and verbal behaviours during episodes of agitation (Stahl et al., 2019). The neurobiology of BPSD involves different brain regions such as cortico-cortical networks and fronto-subcortical circuits. These regions occur alterations of neurotransmitter systems and neurochemical mechanisms. Moreover, there are additional risk factors including a combination of psychological, biological, and environmental variables also contributing to the BPSD. Thus, the treatment of BPSD is challenging due to multiple co-morbidities present in dementia patients with highly variable symptoms and vulnerability factors (Stahl & Morrissette et al., 2014). The Neuropsychiatric Inventory Questionnaire (NPI) is still a reliable resource for evaluating BPSD, not only the range and severity of the behavioural symptoms, but also the impact of such behaviours on caregivers (Stahl et al., 2019). Moreover, recent studies stated that the neurotransmitters for serotonin, noradrenaline, dopamine, acetylcholine, glutamate, gamma-aminobutyric acid (GABA), and sigma receptors in the brain are involved in agitation and aggressive behaviours centralised in the prefrontal cortex of the

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brain (Stahl et al., 2018). Based on these facts, the published experts and the updated guidelines stated that pharmacological interventions for the treatment of agitation and aggressive behaviours should be targeting these neurotransmitters to correct the impairment of top-down cortical control in the brain, and reduce the bottom-up limbic drives (Stahl et al., 2018). To establish this statement in practical way, the first treatment involves non-psychotic based therapies such as antidepressant (e.g. citalopram, escitalopram, sertraline and fluoxetine), adrenergic agents (e.g. clonidine, prazosin), anticonvulsants (e.g. valproate and carbamazepine). These agents are effective to treat agitation as they work effectively on these neurotransmitters are also considered mood stabilisers. They also have a lower side effect profile when compared to antipsychotics (Stahl et al., 2019). The second line measures include an intervention with an antipsychotic treatment. However, despite the initial effectiveness of these agents to treat agitation and psychotic episodes, they still need to be given with caution as they give a greater propensity for motor side effects in patients with Parkinson's dementia or other types of dementia in which movement symptoms pervade (Stahl et al., 2019).

What are the recent trials for the treatment of agitation in dementia?

Antipsychotics

Regarding haloperidol, based on current evidence, the dose of 1.2 to 3.5 mg daily has been found effective in supressing aggressive behaviours, but it shows lower efficacy on agitation. Also noteworthy is that this medication, at this dose has been shown to cause side effects such as extrapyramidal side effects, arrhythmia, and QT prolongation. As a result, prescribing haloperidol to older people for agitation management is not recommended (Masopust et al., 2018). A clinical double-blinded, placebo-controlled trial was conducted comparing efficacy regarding agitation and aggressive behaviours in older persons with dementia by randomly assigning olanzapine, quetiapine, and risperidone. The results of this study stated that clinical benefits were observed only 29% for risperidone, 26% for quetiapine, 32% for olanzapine, and 21% for placebo. As a result, there are significant differences (Maher & Theodore, 2012). In comparison, another trial study called CATIE-AD evaluated the effectiveness of risperidone, quetiapine, olanzapine, and placebo toward aggressive behaviours and agitation in dementia. The results of this study stated that these medications are effective for lowering agitation but not for aggressive behaviours (Sultzer et al., 2008). Moreover, it has been noted by health professionals that higher doses of second generation of antipsychotics are a cause of agranulocytosis (increase susceptibility of infection, especially respiratory infection) and cardiovascular events and metabolic syndrome (Sultzer et al., 2008).

Antidepressants

There are some clinical trials demonstrating evidence of efficacy for selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, and sertraline) for managing agitation in Alzheimer's dementia. The use of citalopram has the most compelling evidence for the treatment of agitation in BPSD. A RCT study compared the efficacy of citalopram, perphenazine and placebo. The result stated that both medications provided more efficacy than the placebo in short-term treatment in a hospital setting, for managing psychotic disturbance including agitation (Pollock et al., 2003). Citalopram has also demonstrated efficacy in lowering agitation scores, this fact is stated by a RCT study conducted a comparison between citalopram and risperidone. The result of this study showed that citalopram lowered the score of agitation compared with other antipsychotics and has less side effects (Pollock et al., 2007). CitAD study published the results of their trial confirming that citalopram can be used for agitation in Alzheimer's dementia, as this medication demonstrated efficacy and a high acceptability rate over placebo (Porsteinsson et al., 2014). Moreover, citalopram has showed similar efficacy against agitation in the longitudinal RCT at nursing homes in comparison with olanzapine and quetiapine. This study also showed that citalopram was associated with lowered occurrence of falls, orthostatic hypotension and hospitalisation over olanzapine and quetiapine (Viscogliosi, Chiriac, & Ettorre, 2017). In general, the American FDA recommend the use of citalopram at 20mg daily as the maximum dose for agitation. One point requiring emphasis regarding citalopram is that this medication takes at least 2-4 weeks to begin showing an observable therapeutic effect. Therefore, it should not be considered for the acute treatment of agitation (Marcum, 2013). The other compared SSRI antidepressant escitalopram showed efficacy and clinical benefits in managing agitation as well. A comparison was made between escitalopram and risperidone in a 6-week clinical trial at a nursing home (Barak, 2014). The results of this study showed both of these agents reduced agitation and noted that risperidone has earlier efficacy in comparison with escitalopram, but it has a larger risk profile for side effects in older people with dementia. Moreover, escitalopram showed cardiovascular events by prolong the QT interval. Therefore, it recommended that

escitalopram might be considered for managing agitation at lower dose of 10mg daily in the elderly (Barak, 2014). Another SSRI antidepressant agent called sertraline also demonstrated efficacy for BPSD by RCT double blinded – placebo-controlled trial. The results of this study demonstrated a decrease in agitation, aggressive behaviours, and psychiatric symptoms in patients with moderate to severe dementia. However, one or only a few clinical trials are not enough to establish evidence of efficacy in agitation management (Lanctot, 2002). Therefore, more RCTs of a longer duration with a larger sample size of older people would be beneficial to better establish the efficacy and safety of sertraline for managing agitation (Lanctot, 2002). Moreover, A 12-week prospective (open label) study trialled the use of Mirtazapine for managing agitation in older people with dementia. The result demonstrated a significant reduction in the Cohen-Mansfield Agitation Inventory Score (CMAI) after treatment at a dose of 15-30mg nocte (Cakir & Kulaksizoglu, 2008). RCT agitation treatment studies using anticonvulsants such as carbamazepine, oxcarbazepine, valproate, gabapentin, levetiracetam, topiramate and lamotrigine found evidence of modest benefits for agitation management and aggressive behaviours in older people in comparison with placebo (Gallagher, & Herrmann, 2014). However, these are also shown to have a plethora of undesirable side effects and the potential harm older people. They also have multiple reported moderate to severe drug-drug interactions and need dosage adjustment for people suffering renal and hepatic impairment, which is common in older people (Gallagher, & Herrmann, 2014).

What are the novel treatments of agitation in dementia?

There are new developments in the treatment of agitation in dementia including the evaluation of new agents with novel therapeutic mechanisms in clinical trials. The most recent agent is brexpiprazole, it is a dopamine 2 partial agonist, and has a multiple 5HT and alpha-adrenergic receptor binding properties. The safety of brexpiprazole has been approved by clinical trials in US for cardiovascular, metabolic effects and the movement risk is acceptable than the other antipsychotic agents. In the future further studies will determine the efficacy and the safety of this agent as it progresses for formal approval by American FDA for the treatment of agitation in dementia (Grossberg, Kohegyi, & Mergel, 2018). The other agent is called dextromethorphan combined with quinidine (DEX-Q). Dextromethorphan is a sigma-1 and mu-opioid receptor agonist, and NMDA (N-Methyl-D-Aspartate) and nicotinic alpha3-beta4 receptors. These receptors inhibit both serotonin and noradrenaline reuptake respectively. Consequently, lowering the agitation and anxiety of the patient (Stahl, 2016). As stated before, the dextromethorphan is combined with quinidine, the purpose of this combination is that quinidine inhibits the cytochrome P450 2D6 enzyme that metabolises the dextromethorphan, thereby will increase the bioavailability of dextromethorphan 20-fold. This combination is approved by FDA for the treatment of pseudobulbar affect, and emotional instability of agitation in Alzheimer's dementia with relatively good tolerability (Stahl, 2016). The third agent is a combination between dextromethorphan and bupropion, a noradrenaline and dopamine reuptake inhibitor and also nicotinic acetylcholine antagonist. Bupropion has the additional pharmacological properties of managing agitation, it also inhibits the capability of CYP 2D6 enzyme, thus inhibiting the metabolism of dextromethorphan (Stahl, 2016). The other agent is Cannabinoid receptors, this agent also having a potential benefit for agitation treatment based on the neuroprotective effects properties. Theta-9-tetrahydrocannabinol, dronabinol and nabilone are the most widely investigated in clinical trials (clinical trial, NCT03328676). Tetrahydrocannabinol failed to show efficacy in reducing agitation or aggressive behaviours, while dronabinol and nabilone showed effects on night-time agitation. The efficacy of these agents was reported in randomised, double blinded, placebo-controlled crossover trials. However, these agents are shown to have side effects causing significant sedation (clinical trial , NCT03328676).

Table 1 is a summary of previous studies in regards antipsychotics for the treatment of agitation in dementia:

Antipsychotic Agents	Type of study	Clinical findings	Adverse events

Haloperidol (Masopust et al., 2018)	Systematic review	Suppresses the aggressiveness behaviours effectively but shows lower efficacy on agitation	Extrapyramidal signs, prolongation of the QTc interval, arrhythmias, and increased mortality.
Olanzapine, Quetiapine, Risperidone, and placebo (Maher, Theodore, 2012)	RCT Double-blind, placebo-controlled trial	No significant difference between the medications for managing agitation, and no significant difference between these medications and placebo	Dysrhythmia and extrapyramidal side effects and delirium
Olanzapine, Quetiapine, Risperidone, and placebo (Sultzer et al., 2008)	CATIE-AD Randomised control- placebo controlled comparative study	The three medications showed the efficacy for managing agitation over placebo.	Increase susceptibility of infection, delirium, cardiovascular events and increase risk of mortality
Quetiapine (Kurlan et al., 2007)	RCT placebo-controlled trial	Quetiapine showed well-tolerated for managing agitation and has no evidence of worsening parkinsonism	Not mentioned
Pimavanserin (Yunusa, Helou, & Alsahali, 2020)	RCT placebo-controlled trial	The study compared the efficacy between 20mg and 34mg of dose to placebo. The results showed the effectiveness of higher dose over placebo at the Phase 3 of this trial	The adverse events at these doses are not established
Brexpiprazole (clinical trials, NCT03548584 and NCT03620981)	RCTs Placebo-controlled trials	The trials tested the efficacy and the safety of 1mg and 2mg of brexpiprazole for managing agitation associated with dementia within 14 weeks treatment. These trials at the stage of phase 3 and ongoing	The adverse events at these doses are not established

Table 2 is a summary of previous studies in regards antidepressants for the treatment of agitation in dementia:

Antidepressant agents	Type of study	Clinical findings	Adverse events
Citalopram (Pollock et al., 2003)	RCT placebo-controlled trial	This study examined the efficacy and the safety of citalopram in agitation. The result stated that citalopram reduced agitation and caregiver distress	The cognitive impairment and cardiovascular events had detected at the dose of 30mg daily
Citalopram, quetiapine, and olanzapine (Pollock et al., 2007)	Randomised controlled trial at nursing homes	The study compared citalopram efficacy and safety with quetiapine and olanzapine. The result stated that citalopram has similar efficacy with quetiapine and olanzapine in managing agitation.	Citalopram provides less adverse effects when compared with olanzapine and quetiapine

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Citalopram and risperidone (Pollock et al., 2007)	RCT comparison between citalopram, risperidone, and placebo effects	The result showed the agitation and psychosis events were decreased in both treatment groups with no significant difference in between.	Citalopram was associated with less adverse events in comparison with risperidone
Citalopram and perphenazine (Pollock et al., 2003)	RCT placebo-controlled trial in hospitals	The result stated that both agents were significantly improved the agitation compared to placebo. Moreover, citalopram found to be more efficacious in short-term of psychosis treatment in hospitals	Citalopram provided less adverse effects compared with perphenazine
Escitalopram and risperidone (Barak et al., 2011)	RCT assigned two groups in hospitalised patients with dementia	The results stated that there is no significant difference between escitalopram and risperidone in the efficacy of managing agitation	Escitalopram provides less side effects than risperidone
Sertraline, risperidone, and placebo (Lanctot et al., 2002)	RCT placebo-controlled trial assigned groups	Both agents are lowering the agitation and aggressive behaviours. But Sertraline takes longer to be effective compared with risperidone	Not mentioned
Mirtazapine (Cakir, & Kulaksizoglu, 2008)	RCT placebo-controlled trial	The results demonstrated the efficacy for the treatment of agitation with dementia and no significant side effects and cognitive deteriorations	Sedation and risk of falls

The benefits of this narrative review

Agitation is a common feature observed in aged care facilities and in hospitals. Also, the causes of agitation may not always be observed. In regard to mild agitation, it can be managed by non-pharmacological interventions with non-coercive treatment, but it becomes severe, the pharmacological interventions need to be necessary to use. From an intensive review in regards the efficacy and the safety of the different classes of the medications, it becomes clear that the antipsychotic medications provide onset management of agitation and suppress the aggressiveness, however, these agents providing undesirable side effects and adverse events to fragile people like older people with dementia and chronic conditions. Therefore, failure to find disease modifying treatment for dementia has driven clinicians to find better symptomatic management for BPSD, especially for agitation episodes. Currently the medication classes available for treatment of agitation are antipsychotics and benzodiazepines. These treatments have some serious adverse effects for older people, and there is evidence suggesting these medications are involved in the progression of cognitive decline and contribute to the development of metabolic and cardiovascular diseases. Moreover, from previous systematic reviews which evaluates evidence from RCTs, systematic reviews, and meta-analyses of BPSD patients who have taken agitation treatments. Assessing the efficacy of selective serotonin reuptake inhibitors (SSRI) and antipsychotic treatments, when compared to each other for the purpose of improving agitation outcomes. The main conclusion of these reviews stated that there are still limited studies involving SSRIs for the treatment of agitation in BPSD. SSRIs such as citalopram were associated with a reduction in symptoms of agitation, and lower risk of adverse effects when compared to antipsychotics. Future studies are required to assess the long-term safety and efficacy of SSRI and antipsychotics as treatments for agitation in BPSD. In addition, there is currently no studies on Australian aged care residents, comparing the efficacy and safety between antipsychotics and SSRIs for managing BPSD associated agitation.

What are journal articles that presented data the efficacy and safety of psychotropics retrospectively?

There is as yet no study comparing the efficacy and safety between antipsychotics and SSRIs in managing agitation of dementia in Australia. There is also a paucity of valid evidence, examining SSRIs for the treatment of agitation in dementia. The research which is available identifies a need for further studies to examine the efficacy and the safety of antipsychotics and SSRIs in aged care residents involving more participants in different facilities. To establish this research in a practical way, a retrospective study is the best option to start to assess the safety and efficacy of antipsychotics and antidepressants, after establishing a well-designed document of results, the prospective study will be proposed thereafter to improve outcomes for residents with dementia, suffering episodes of agitation and/or psychosis in Australian Aged Care Facilities. There are only four published clinical studies are similar to the nature and design of our project. None of these previous studies were conducted in Australia. Therefore, our study is a nationally unique project will be conducted in aged care facilities. Trinkley et al. 2020, designed a retrospective observational study performed by reviewing medical records. Patients diagnosed with dementia and reported to experience BPSD episodes, including symptoms of agitation, psychosis, and hyperkinetic behaviours, all received documented treatment with atypical antipsychotics for at least 2 weeks. The sample size of this study was 81 patients were included, all satisfied the inclusion criteria, and researchers had full access to medical records. The study tested the efficacy and the safety of atypical antipsychotics. The study looked at 3 dosage ranges for atypical antipsychotics: low, medium, high, and compared the effects of each dosage level. All symptoms, specifically behaviours were assessed before commencing and following 2 weeks of the treatment protocol. The impact of treatment was assessed by comparing the duration of treatment to documented behavioural and psychological changes in participants (the parameters were categorised as: improved, stable, and worsened). Moreover, the study measured the safety of the atypical antipsychotics by using laboratory values records of linked adverse effects, therapeutic response, reason of discontinuation and changes to other psychotropic interventions. Furthermore, the study compared the duration of the atypical antipsychotic administration with the frequency of adverse effects among the participants. The adverse events are categorised into metabolic issues, falls, extrapyramidal side effects, cardiovascular events, and mortality. the results of this study stated that atypical antipsychotics improved the symptoms of BPSD and observed a high frequency medication related adverse events. This statement matched the papers introductory statement, which indicated that previous studies found same issues. Furthermore, the previous studies mentioned in the introduction part stated, “further studies need to be performed to evaluate the efficacy and safety of atypical antipsychotics for managing BPSD”, and this paper satisfied recommendations made by the previous studies. The conclusion only emphasised the risks of atypical anti-psychotics. The statement in the conclusion does not reflect the whole results and the outcome of this study, and it does not mention the benefits versus risk of atypical antipsychotics. Moreover, the recommendations in regard to further prospective studies, longer duration of study and the potential designs of RCTs are mentioned in the last part of discussion.

The other study conducted by Schnelli et al. 2021. The method of study is a retrospective cross-sectional study conducted by reviewing patient’s data history. The population of study is residents in aged care homes with documented aggressive behaviours towards health care staff. Retrospectively collected data of 1186 residents from six recruited home care services. The data was collected between July 2019 to September 2019. This study comprehensively reviewed the frequency and types of aggressive behaviours expressed by cognitively impaired residents toward health professionals in aged care facilities. The paper also illustrated using statistics that aggressive behaviours in numerous ways cause stress to the health care professionals experiencing the aggression, and consequently, impact negatively on the quality of care provided. Moreover, this paper revealed the importance of specialised educational and interventional training for health care professionals to improve ongoing care in nursing homes. The conclusion of this study stated that verbal aggressive behaviours are the most common, and frequently recorded in people that have limited communication and higher dependency on others. Also, this paper was established to be robust and applicable to clinical practice. The authors detailed in the last paragraph opportunities for further clinical research, proposing ways to include educational interventions for nursing staff, focussed on interactions with patients who have a dementia diagnosis, communication limitations, and are reported to display aggressive behaviours.

The third clinical study was conducted by Lim et al. 2018. A retrospective study was made up entirely of persons with diagnosed dementia, and is separated into age categories. From the total of 155 dementia residents. 77 were >85y.o. and 78 were <85y.o. A good group division would be at least 10%. In this study, the sample groups are equal at 50% of the total population. The samples groups are completely relevant to the population, as these age groups represent the average population within residential aged care facilities. This study compared the efficacy and adverse effects of anti-dementia drugs between an over 85y.o. group and younger than 85y.o. group. Also verified baseline characteristics and initial neuropsychological symptoms within the groups. In

the introduction part, it was presumed that the adverse effects of the anti-dementia agents would be higher in the group of older than 85y.o. But the results of this study indicated no difference, as mentioned in the discussion. Furthermore, the efficacy of anti-dementia drugs in the change of cognition and quality of life was not different compared between the two groups, while the cognitive decline, K-MMSE score and CDR, I-ADL scores were higher in group of older than 85y.o. In general, the authors reflections addressed the issues in the introduction and explained the results in comprehensive manner. The researchers have made their arguments based on results that had no significant differences between the two sample groups, and argues that age should not be a major contributing factor when prescribing anti-dementia agents. The research was unable to determine a significant difference in adverse effects profiles of anti-dementia agents, when using age as a comparison. There is no significant difference according to these results in the efficacy of anti-dementia agents when comparing participants based on age.

The last paper was published by Aigbogun et al. 2020. This nature of this study is a retrospective observational medical history chart review. 801 patients with dementia were divided into 2 groups: 312 aged care residents and 489 community-based residents. The aged range was between 55 to 90 years old and had commenced use of antipsychotics for the treatment of agitation. The data was collected between January 2018 and May 2018. The two sample groups accurately reflect the general population of persons diagnosed with dementia. There is a strong correlation between the information contained in the discussion and the study results. The discussion contains detail about the use of non-pharmacological interventions including supporting evidence from previous clinical trials and systematic reviews. Also, this study determined the use of a non-pharmacological approach was low among both care settings, due to lack of training for physicians and care givers. The pharmacological, antipsychotic interventions are illustrated in detail and supported by the statistical outcomes of this study. It also discussed the correlation between the antipsychotic effects and the metabolic issues post administration. Overall, the discussion part of this study provides only a generalised overview of the results. Moreover, there are no details about which kind of non-pharmacological intervention and the criteria for those interventions. Most of the patients in this study started their antipsychotics after several episodes of agitation, without a trial period of non-pharmacological interventions. This study found that guidelines and recommendations for non-pharmacological interventions was not adequately followed by clinicians. Moreover, the study provides in-depth discussion about the burdens of agitation to both carers and health professionals and gives hints to the researcher for establishing effective agitation management. The conclusion reflects the results, and how the outcome reflects on the inadequate follow through for non-pharmacological treatment plans and their role in agitation management. But contains no details about pharmacological options or their efficacy in management of agitation. The authors have not made any recommendations beyond the focused subject.

Table 3: the comparison between the four studies and our project

Features	Trinkley et al. 2020	Schnelli et al. 2021	Lim et al. 2018	Aigbogun et al. 2020
Type of study	Retrospective	Retrospective observational	Retrospective	Retrospective
Focused subject	Atypical antipsychotics	Psychotropic in general	Anti-dementia drugs	Antipsychotics and non-pharmacological interventions
Type of mental issues	BPSD with agitation and psychosis episodes	Aggressive behaviours and agitation by the residents against health professional caregivers	Dementia with aggressive and agitation records	Dementia with BPSD
Type of investigation	Investigated the efficacy and safety of only atypical antipsychotics	Investigated the efficacy and safety of psychotropics in general	Investigated and compared the efficacy and adverse effects of anti-dementia drugs	Investigated the efficacy of commenced use of antipsychotics for the treatment of agitation.

Methodology	Collected the records of out-patients who satisfied the inclusion criteria and retrospectively reviewed from 1990 to 2010	Collected the nursing home residents' records between July 2019 to Sep 2019,	Collected the nursing home records and review it retrospectively	Collected the nursing home records and review it retrospectively

Conclusion

BPSD are still a significant problem in everyday practice at nursing homes and in hospitals. To date, the precise and useful recommendations in regards agitation treatments are still lacking. In clinical practice, many pharmacological options are using for managing agitation. Unfortunately, physicians are still using antipsychotics for agitation despite of undesirable side effects, and lack of strong evidence confirming their effectiveness. As a result, there is a continued pushing to reduce the use of antipsychotics in older people and using alternative agents such as mood stabilisers and SSRIs. Although few evidence had been collected in this review, the findings from the two systematic reviews and the three clinical trials indicated that SSRI antidepressants (e.g., citalopram) not only showed efficacy for treating BPSD but also tolerated compared to antipsychotics. This review also presented that citalopram reduces the symptoms of agitation when compared to placebo and it has less adverse effects comparing with atypical antipsychotics such as risperidone, quetiapine, and olanzapine. This review describes some novel treatments for the symptomatic treatment of agitation in Alzheimer disease recently entering clinical practice in the US. This review describes the efficacy of SSRIs targeting serotonin for the symptomatic treatment of psychosis in dementia; and illustrates brexpiprazole as a target of multimodal neurotransmitters such as dopamine, serotonin and norepinephrine; and dextromethorphan, OR dextromethorphan associated with bupropion or quinidine as a blockade of NMDA receptors. The outcome of this review suggests that further studies involving more dementia/Alzheimer's participants from aged care facilities should be conducted. Future studies are required also to assess the long-term safety and efficacy of SSRI, brexpiprazole, dextromethorphan treatments for agitation in BPSD. The outcome of this review suggested further studies involving more participants from aged care facilities, longer duration of the trial to assess the safety and the efficacy of citalopram for managing agitation in dementia in long term us.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, H.Q. and M.S.; methodology, H.Q.; validation, H.Q., M.S. ; formal analysis, H.Q.; investigation, H.Q., M.S.; resources, H.Q.; data curation, H.Q., M.S.; writing—original draft preparation, H.Q.; writing—review and editing, H.Q., M.S.; supervision, H.Q., M.S. All authors have read and agreed to the published version of the manuscript."

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Conflict of interest

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