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Review Article

Risk of Cerebrovascular Events Associated with Antipsychotics in Dementia: A Systematic Review

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Abstract

Background: Antipsychotics have been used for many years for the treatment of neurological disorders, and the application of antipsychotics in the elderly have increased in frequency over the past few years. The absolute benefit of typical as well as atypical antipsychotics have come into question as their safety in elderly population is not seem to be in sync with their theoretical assessments.

Purpose and Objective: To understand the various side effects, or adverse events, associated with the use of typical and atypical antipsychotics. To assess the benefits and risks of use of typical and atypical antipsychotics through risks vs. benefits, morbidity and mortality through a secondary search analysis of various randomized clinical trials.

Design: The research was conducted through PubMed, MEDLINE, and Google Scholar, where keywords used to search for studies were 'antipsychotics', 'dementia', 'elderly', 'typical antipsychotics', 'atypical antipsychotics', 'psychosis', 'risks', 'benefit', 'behavioral disorders', and 'adverse cerebrovascular events'.

Findings: 8 studies were selected for the review that matched the inclusion criteria of the study. The studies included a total of 3135 elderly patients with dementia of the Alzheimer's type, vascular dementia and mixed dementia, with mean age 80.4 years. The studies evaluated provided the benefits of antipsychotics, their relative risks and the side effects related to cerebrovascular events.

Conclusion: The findings of this study led to the understanding that there was no significant difference between typical and atypical antipsychotics in terms of efficacy, and that higher dose of antipsychotic lead to greater number of adverse events in the elderly patients. Also, cerebrovascular events was not a significant adverse event in the treatment groups, as somnolence and gait disturbances were more common and frequent than stroke and ischemic attacks. Thus, these antipsychotics pose a moderate risk in terms of cerebrovascular health of patients suffering from dementia.

Keywords: *Antipsychotics; Typical Antipsychotics; Atypical Antipsychotics; Cerebrovascular Events; Dementia; Randomized Controlled Trials*

Introduction

Dementia is a neurological disorder characterized with behavioral and psychological symptoms which interfere with normal functioning of a person, by disrupting the daily activities. The global burden of dementia is around 46 million, which is expected to rise to 131 million by the year 2050 [1]. Alzheimer's disease is found to be the most common form of dementia, and some estimates also suggest that the rate of increase of dementia incidence is more than double in the present time. The behavioral symptoms as well as psychiatric symptoms that are part of dementia develop in almost 60% of patients living in communities, while 80% of nursing home patients develop these symptoms [2]. The lifetime risks of behavioral and psychiatric symptoms develop up to 100%, when this disease remains unchecked and

untreated. In terms of treatment scenario of dementia, there is no apparent cure for this disease and with the increasing elderly population over the globe, it is a very serious concern in terms of dementia management and prevention [3,4].

Clinical Use of Typical and Atypical Antipsychotics in Elderly People

The advent of antipsychotics provided a way for prescribers to manage the behavioral and psychotic symptoms of patients suffering from dementia. The first dopamine blocking conventional, or typical, antipsychotic that was discovered was chlorpromazine in 1952. This drug was mainly used to treat schizophrenia, and drastically changed the treatment scenario of neurodegenerative disorders [5,6]. The discovery of this conventional antipsychotic led to the discovery of many other compounds and typical antipsychotics were thus available to treat patients with mental disorders for more than 5 decades. The other drugs such as haloperidol and Loxapine came in the later stages, but shared the same characteristic of being dopamine receptor inhibitors of the brain, especially the D2 receptor [7]. The activity of inhibition conferred them the ability to repress symptoms of mental disorder, but these drugs also had their own side effects. The drugs of the typical antipsychotic class were although effective on the positive symptoms of dementia, schizophrenia and Alzheimer's disease, but they also caused certain side effects such as sedation, anti-cholinergic toxicity, glaucoma, cerebrovascular events such as stroke, and extrapyramidal symptoms including Parkinsonism and dystonia [8]. These side effects are more common in the elderly population as this population is more susceptible to these drugs. The typical antipsychotics were then followed by the advent of atypical antipsychotics to increase efficacy in controlling negative symptoms of dementia and better manage the extrapyramidal symptoms that the typical antipsychotics induced [9]. The first atypical antipsychotic to gain FDA approval was clozapine in 1989. Other antipsychotics followed in the following years: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), and aripiprazole (2002) [10]. These drugs were capable of providing lower risks to motor adverse effects and improved tolerability and better efficacy than the typical counterparts. The various typical and atypical antipsychotics with their starting doses and maintenance doses are mentioned in table 1.

Antipsychotic	Type of Antipsychotic	Starting Dose (mg/day)	Maintenance Dose (mg/day)
Haloperidol	Typical	0.25 - 0.5	1 - 3.5
Thioridazine	Typical	10 - 25	50 - 100
Clozapine	Atypical	6.25 - 12.5	50 - 100
Risperidone	Atypical	0.25 - 0.5	1 - 2.5
Olanzapine	Atypical	1 - 5	5 - 15
Quetiapine	Atypical	12.5 - 25	75 - 125

Table 1: *Usual recommended doses of common antipsychotic drugs for elderly patients.*

The atypical antipsychotics were also used for a wider variety of indications, especially in those patients who were more susceptible to motor side effects while using typical agents. It has been noted that the highest number of prescriptions related to neurological disorders in elderly patients are for behavioral disturbances associated with dementia [11]. These drugs then became the means for treating symptoms of dementia as well as other psychotic disorders; however, these drugs were also not free from controversy. Many researchers reported adverse events related to atypical antipsychotics use in elderly patients suffering from dementia [8,12]. In elderly patients, the use of typical antipsychotics have demonstrated increased risk of mortality, which is 1.5 - 1.7 times higher when compared to patients receiving no medication [13]. Keeping in regard this increased risk of adverse events related to cerebrovascular events, the FDA has issued the companies the directive to use a black box warning notifying the patients and caregivers about the risks that these antipsychotics present to the patients, apart from the positives and benefits that these drugs confer among the patients suffering from various forms of dementia [9]. In case of atypical antipsychotics, the risk is also 2 - 3 folds in terms of cerebrovascular events (CVAE), which leads the drugs to have an absolute risk of approximately 1% in patients suffering from dementia and other forms of neurological disorders [8].

The aim of the study is to observe the risk of cerebrovascular events associated with the use of atypical and typical antipsychotics, in elderly patients suffering from dementia, as reported by the clinical trial studies. Apart from this, the objectives of the study are:

- To understand the clinical use of antipsychotics to assess their needs and use in patients with dementia.
- To assess the risks and benefits of the treatment provided by typical and atypical antipsychotics in patients suffering from dementia.

Methodology

Research Design

The present paper is a systematic review of studies involving randomized controlled trials, carried out to assess the impact of antipsychotics in the elderly patients suffering from dementia. Thus, this study was conducted and research papers of randomized control trials were filtered from other research results by following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The search was done through PubMed, Medline, Google Scholar and EMBASE to search for relevant studies of antipsychotic use in dementia. Also, studies were extracted after reviewing abstracts and full text articles related to antipsychotic use in dementia, and the extracted citations were processed through the same guidelines of PRISMA before including them into the study.

Inclusion and Exclusion Criteria

Inclusion criteria

- Studies reporting randomized control trials, where the patients were treated with either typical or atypical antipsychotics or both for assessment of their efficacy and tolerability.
- Studies including patients suffering from one or other forms of dementia only.
- Studies assessing the side effects of antipsychotics related to cerebrovascular events, among other events discussed after assessment of the drug efficacy and tolerability.
- Studies that are written in English, or have official English translations available were included in the study.

Exclusion criteria

- Studies pertaining to other research designs such as cohort studies, case-control study, cross-sectional study, or case reports series.
- Studies including patients suffering from other mental illnesses such as Schizophrenia, bipolar disorder, anxiety disorder, among others.
- Studies reporting that have only qualitative assessment of efficacy of antipsychotics.

Study Selection

The study selection was done by searching research papers of various journals through search of different electronic databases, such as PubMed, Cochrane Review Library, EMBASE and PubMed Central by using different keywords such as 'antipsychotics', 'dementia', 'elderly', 'typical antipsychotics', 'atypical antipsychotics', 'psychosis', 'risks', 'benefit', 'behavioral disorders', and 'adverse cerebrovascular events'.

Individual Keywords	Combined Keywords
Antipsychotics	Risks typical antipsychotics
Dementia	Risks atypical antipsychotics
Elderly	Benefits typical antipsychotics
Typical antipsychotics	Benefits atypical antipsychotics
Atypical antipsychotics	Benefits atypical antipsychotics dementia elderly
Adverse cerebrovascular events	Risks atypical antipsychotics dementia elderly
	Benefits typical antipsychotics dementia elderly
	Risks typical antipsychotics dementia elderly
	Adverse cerebrovascular events antipsychotics dementia

Table 2: *Keywords used for performing database search.*

The duplicates gained through various searches were removed. Once the records with unique titles were left the studies were again filtered as to exclude studies such as cohort studies or non-pharmacological intervention, journal articles were also excluded. The remaining full-text articles were evaluated by the researchers for further progression of the study.

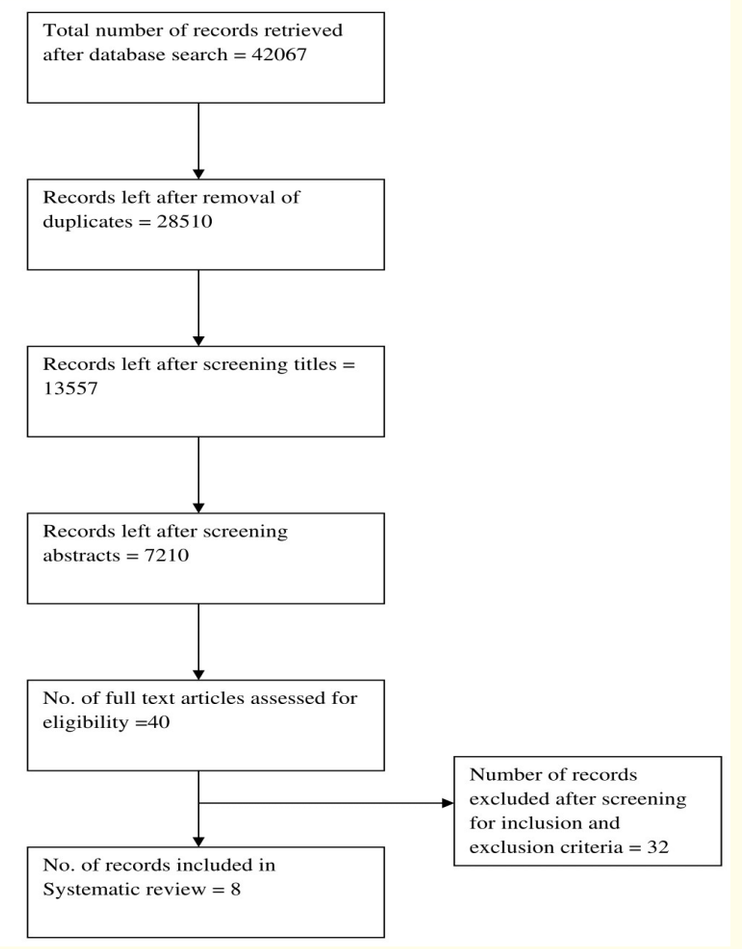

Figure 1: *Prisma Flow Diagram for the Study.*

Data Extraction

The data needed for the study was extracted from the collected research papers as per the relevance of the material. The data pertaining to patient demographics, the antipsychotic type and names of the antipsychotics, the mean dose of the drug, the evaluation criteria, the efficacy results, and the side effects was extracted. The data extracted was then analyzed through content and critical analysis to create an analytical assessment of the effect of antipsychotic use on the mental health and overall health of the patients. The study also, through this analysis, identified the instances and severity of the side effects in patients enrolled in various studies.

Systematic Review Analysis

Search Results

8 randomized control trials were finally selected for this study, and all included elderly patients suffering from Dementia. To summarize, 5 trials [3-6,15-17] enrolled patients diagnosed with Dementia of the Alzheimer's type, 5 trials enrolled patients diagnosed with Alzheimer's disease [16,18-21] with psychosis and/or aggravated and agitated behavior, 5 trials enrolled patients of vascular dementia, and 5 trials enrolled patients with mixed dementia [3,4,17,21-23].

All trials enrolled a total of 3135 elderly patients, with mean age 80.4 years, with 2179 females, while the total number of men enrolled in these trials was 956. The trials duration ranged from 3 weeks to 36 weeks, with 1933 patients on drug treatment arm and 1201 on placebo treatment arm. The main objective of all the trials was to assess the safety and efficacy of the use of typical or atypical antipsychotics, in comparison to placebo or an active comparator, where the outcome measures varied from change in psychiatric and behavioral symptoms to functional abilities to quality of life to even mortality. The side effects that were assessed in the trials included extrapyramidal symptoms, cerebrovascular events such as stroke and death, somnolence, and gait disturbances. The results of the study search conducted by the researcher are tabulated in the systemic review table in the following section.

Systematic Review

Author (Year); Country	Trial Duration	Total number of patients	No. of Patients in treatment arm	Type of drugs administered
Deberdt., *et al*. (2005); USA	10 weeks	494	Olanzapine = 204 Risperidone = 196 Placebo = 94	Atypical
(Brodaty., *et al*.., 2003); Australia	12 weeks	301	Risperidone = 149 Placebo = 152	Atypical
(Katz., *et al*.., 1999); USA	12 weeks	625	Risperidone = 312 Placebo =312	Atypical
(Mintzer., *et al*.., 2006); USA	8 weeks	473	Risperidone = 235 Placebo = 238	Atypical
Mintzer., *et al*. (2007); USA	10 weeks	487	Aripiprazole = 366 Placebo = 121	Atypical
Ballard., *et al*. 2008	12months	165	Active treatment = 83 Placebo = 82	Atypical = Risperidone Typical = Chlorpromazine, haloperidol, trifluoperazine
Allain., *et al*. (1999); France	3 weeks	306	Active treatment = 203 Placebo = 103	Atypical = Tiapride Typical = Haloperidol
Tariot., *et al*. (2006); USA	10 weeks	284	Quetiapine = 91 Haloperidol = 94 Placebo = 99	Atypical = Quetiapine Typical = Haloperidol

Table 3: *Characteristics of studies included in the systematic review.*

Author (Year); Country	Patient Demographics					
	Age	Mean Dosage of drug:	Females/ Males	Type of dementia		
				Alzheimer	Vascular	Mixed
Deberdt., *et al*. (2005); USA	Olanzapine = 77.9 (7.7) Risperidone = 78 (6.9) Placebo = 79.8 (7.2)	Olanzapine = 2.5 mg–10 mg/day Risperidone = 0.5 mg–2 mg/day	Olanzapine = 141/63 Risperidone = 123/73 Placebo = 60/34	Olanzapine = 158 Risperidone = 166 Placebo = 78	Olanzapine = 11 Risperidone = 11 Placebo = 6	Olanzapine = 35 Risperidone = 19 Placebo = 10
(Brodaty., *et al.* 2003); Australia	Risperidone = 83.2 (0.51) Placebo = 82.7 (0.64)	Risperidone = 0.95 mg/day	Risperidone = 109/44 Placebo = 113/43	Risperidone = 87 Placebo = 93	Risperidone = 44 Placebo = 44	Risperidone = 22 Placebo = 19
(Katz., *et al.* 1999); USA	82.7 years	0.5 - 2mg/day	423/201	469	94	75
(Mintzer., *et al.* 2006); USA	Risperidone = 83.4 (7.2) Placebo = 83.2 (7.38)	Risperidone = 1.03 (0.24)	Risperidone = 183/52 Placebo = 181/57	Risperidone = 204 Placebo = 213	Risperidone = 31 Placebo = 25	
Mintzer., *et al*. (2007); USA	Aripiprazole (2 mg/day)= 83 (62-95) Aripiprazole (5 mg/day) = 82.4 (60-97) Aripiprazole (10 mg/day) = 82.3 (56-94) Placebo = 82.2 (56-96)	Aripiprazole = 2;5&10 mg/day	Aripiprazole (2mg/day) = 81/19 Aripiprazole (5mg/day) = 76/24 Aripiprazole (10mg/day) = 76/24 Placebo = 82.2 (56-96) = 82/18	Alzheimer's Disease		
Ballard., *et al*. 2008	Active treatment = 84.8 (7.0) Placebo = 84.9 (6.1)	Risperidone = 0.5 - 1mg/day Chlorpromazine = 12.5 - 25 mg/day Haloperidol = 0.75 - 1.5 mg/day Trifluoperazine = 0.5 - 1 mg/day	Active treatment = 64/19 Placebo = 62/20	Alzheimer's Disease		
Allain., *et al*. (1999); France	Tiapride = 80.3 ± 7.6 Haloperidol = 79.9 ± 7.9 Placebo = 78.6 ± 7.3	Tiapride = 175.45 ± 44.70 Haloperidol = 3.53 ± 1.05	Tiapride = 63/39 Haloperidol = 63/38 Placebo = 71/32	Alzheimer's Disease		
Tariot., *et al*. (2006); USA	Quetiapine = 81.92 (6.85) Haloperidol = 83.55 (6.05) Placebo = 83.93 (6.66)	Quetiapine = 91 Haloperidol = 94 Placebo = 99	Quetiapine = 66/25 Haloperidol = 63/91 Placebo = 79/20	Alzheimer's Disease		

Table 4: *Patient characteristics of the studies included in the systematic review.*

Author (Year); Country	MMSE scores		Adverse events	Adverse events of special focus	
	Baseline	Final/Change		Cerebrovascular events	Mortality
Deberdt., *et al*. (2005); USA	14.4(5.6)	Olanzapine = 14 (5.4) Risperidone = 14.7 (5.5) Placebo = 15.2 (6.2)	Somnolence, agitation, confusion, accidental injury, hallucinations, abnormal gait, urinary incontinence, delusions, nervousness, asthenia, hostility, insomnia, anorexia, dizziness, peripheral edema, weight gain, flu, dyspnea	Olanzapine = 2.5% Risperidone = 2% Placebo = 0%	Olanzapine = 2.9% Risperidone = 2% Placebo = 1.1%
(Brodaty., *et al*.., 2003); Australia	Risperidone = 5.14 (0.45) Placebo = 5.78 (0.46)	No change	Somnolence, agitation, confusion, accidental injury, hallucinations, abnormal gait, urinary incontinence, delusions, nervousness	Risperidone = 6	Risperidone = 6 Placebo = 10
(Katz., *et al*.., 1999); USA			Extrapyramidal symptoms, somnolence, and mild peripheral edema	CVAE reported	
(Mintzer., *et al*.., 2006); USA	Risperidone =13.2 (4.93) Placebo = 13.2 (5.01)			Risperidone = 4 Placebo = 1	Risperidone = 9 Placebo = 6
Mintzer., *et al*. (2007); USA	Aripiprazole (2 mg/day) = 12.2 (8.0) Aripiprazole (5 mg/day) = 12.4 (8.2) Aripiprazole (10 mg/day) = 13(8.0) Placebo = 11.7 (8.2)	Aripiprazole (2 mg/day) = - 0.3 (6.2) Aripiprazole (5 mg/day) = - 1.6 (7.0) Aripiprazole (10 mg/day) = -1.0 (7.4) Placebo = - 0.9 (6.2)	Somnolence, agitation, confusion, accidental injury, hallucinations, abnormal gait, urinary incontinence, delusions, nervousness, asthenia, hostility, insomnia, anorexia, dizziness, peripheral edema, weight gain, flu, dyspnea, ecchymosis, rash, back pain, abdominal pain, confusion, infection	Aripiprazole (2 mg/day) = 1 Aripiprazole (5 mg/day) = 2 Aripiprazole (10 mg/day) = 4 Placebo = 0	Aripiprazole (2 mg/day) = 4 Aripiprazole (5 mg/day) = 3 Aripiprazole (10 mg/day) = 8 Placebo = 3
Ballard., *et al*. 2008			Mortality	No significant cerebrovascular events	Increase in mortality over the 12 months of trial, with 5-8% greater increase in patients receiving antipsychotics than those receiving placebo.
Allain., *et al*. (1999); France			Impaired concentration, Asthenia, Sleepiness, Amnesia, Nervousness, Somnolence, Sleep decreased, Indifference, Dystonia, Muscle rigidity, Hypokinesia, autonomic events	No significant cerebrovascular events	Placebo = 4 Tiapride = 1 Haloperidol = 1
Tariot., *et al*. (2006); USA	Quetiapine = 12.40 (5.09) Haloperidol = 12.73 (5.60) Placebo = 13.15 (5.44)	Quetiapine = -1.58 (2.98) Haloperidol = -1.06 (4.26) Placebo = -0.90 (4.42)	Somnolence, Infection, Rash, Pain, Vomiting, Agitation, Urinary tract infection, Agitation, Fever, Pharyngitis, Abnormal gait, Accidental injuries, Falls	Quetiapine = 2 Haloperidol = 1 Placebo = 1	Haloperidol = 2

Table 5: *Treatment outcomes as reported in the studies included in the systematic review.*

Systematic Analysis

The systematic analysis of the literature led to the following findings presented in the form of distinct themes as below.

Typical Vs. Atypical Antipsychotics: Comparison of Risks and Benefits between Two Classes

The second generation, atypical antipsychotics have over the time become preferred pharmacological approach for the treatment of dementia, in elderly patients [24]. A comparative analysis of the risks and benefits associated with the two classes of drugs shows that the atypical antipsychotics have comparable efficacy concerning the typical antipsychotics. However, they are characterized with decreased incidences of side effects and adverse events, hence preferred for use in patients with dementia [25]. Allain., *et al*. [18] illustrated upon the same by conducting a randomized, double blind trial to assess and compare the efficacy of haloperidol, a typical antipsychotic drug, with

Tiapride, atypical antipsychotic, with placebo treatment. The findings from the trial showed no significant difference between the efficacy profiles of the two active drugs, and statistical superiority of both the drugs over the placebo arm was observed.

None of the drugs showed any adverse effects with respect to the cognitive function of the patients, however the numbers of adverse events in Tiapride group (62 patients, 61%, 212 events) were found to be smaller in comparison to the haloperidol group of patients (77 patients, 76%, 305 events). The haloperidol treatment exhibited the highest number of adverse events, with the placebo arm reporting 234 adverse events in 67% of the patients. Although, there was no significant difference in the occurrence of side effects between the two drugs, Tiapride showed better safety profile. The patients tolerated both the drugs in a similar fashion, and showed comparatively lesser extrapyramidal symptoms as compared to the placebo group. The high occurrence of side effects associated with the administration of Haloperidol, in comparison with Risperidone and placebo arms has also been reported by other authors. 80% of the patients who were administered haloperidol reported adverse events, followed by 76.5% and 72.8% in risperidone and placebo arms respectively. They also reported significant improvement with risperidone in comparison to haloperidol [26].

The typical antipsychotics such as Haloperidol have been identified to cause distressing side effects such as akathisia, neuroleptic malignant syndrome, dystonic reaction, motor restlessness, and thereby aggravate the behavioral disturbances. Hence, the typical antipsychotics are not preferred for treating elderly with dementia [27]. The trial conducted by Tariot., *et al.* [28] compared the efficacy of haloperidol with Quetiapine, assessing the efficacy and safety of the two drugs concerning the psychotic symptoms presented by the patients. The Quetiapine, haloperidol and placebo arms showed no significant differences concerning CGI-S and LOCF scores, whereas BPRS scores for treatment with active drugs showed significant reduction from placebo.

Here also, the efficacy profiles were not significantly different from each other, and a similar trend of the high degree of side effects with haloperidol was observed. The patients treated with haloperidol were found to have worst functional outcomes, and showed higher tendencies of developing anergia with none of the active agents were found to bring relief in the psychotic symptoms. However, the evidence from the clinical trials are yet to explicitly address the benefits that are associated with atypical drugs, and the present studies were able to assess was that atypical antipsychotics were less likely to cause adverse events as compared to typical antipsychotics; otherwise, there are no other benefits that are associated with atypical drugs. Also, typical drugs are less expensive and have fewer chances of causing anti-cholinergic, hypotensive, metabolic side effects such, when these are compared to some individual atypical agents.

The lack of randomized drug-controlled trials that and long term follow up studies, present a lack of evidence to assess the effectiveness of these drugs [12]. Also, it has been noted that the available data lacks consistency, the placebo arm has comparable results, and the patients are kept on treatment regimen even in the absence of any benefits from the drug, which does not lead to apt assessment of effectiveness profile [29]. There have been very less studies that compare typical and atypical antipsychotics [17]. Out of the studies that do compare typical and atypical antipsychotics, there is only one study that provides results that atypical antipsychotics are better in efficacy than typical antipsychotics, rest all have proved that there is no significant difference in efficacy between the two classes [3,4].

Benefits of Antipsychotics in Dementia

The symptoms of dementia could be divided psychosis and aggression, or agitation and other behavioral disturbances. The symptomatic antipsychotic treatments have been studied by many researchers through clinical studies. The randomized controlled study results have over the time shown atypical antipsychotics to be effective in treating the psychotic symptoms of dementia Alzheimer's type [30,31]. One such study conducted by Brodaty., *et al*. [15] followed a randomized, double-blinded fashion, to study the efficacy of risperidone for treating aggression, psychosis, and agitation in elderly dementia patients. The result of this study showed that there was a significant difference in the CMAI total aggression score, which provided insight that there was a significant reduction in the aggressive behavior of dementia patients who were in the risperidone group, as compared to placebo. The BEHAVE-AD showed decreased psychotic symptoms, where the CGI-S scales are showing increased improvement of the symptoms of the risperidone group with the placebo group.

Another study conducted by Katz., *et al*. [19] was aimed at assessing the efficacy and safety of risperidone in institutionalized patients diagnosed with dementia, reporting results regarding BEHAVE-AD. The scores indicated a significant difference between patients of risperidone arm, and placebo group, indicating that risperidone was effective in controlling psychotic and behavioral symptoms. However, the findings of clinical trials conducted by [23] reported insignificant improvements in the BEHAVE-AD score within the risperidone and placebo treatment arms. The trial assessed that there were no significant differences between risperidone and placebo in terms of efficacy. It was a unique finding in itself as previous studies had provided ample evidence of superior efficacy of risperidone in managing psychotic symptoms related to dementia.

The MMSE scores were found to show significant differences, with the risperidone treatment showing improvement over placebo. The trial also proved the tolerability and safety of risperidone as there was no increase in falls and agitation, and the tolerability of the drug was comparable to the set FDA standards for atypical antipsychotics. It has also been reported that risperidone might prove to be more efficacious in individuals suffering from severe baseline aggression with respect to those suffering from mild to moderate forms of the disease [32]. Such a finding, supported with additional evidences might help in optimization of suitable drug dosage. Deberdt., *et al*. [33] in a 10 week double blind flexible dose treatment, involving the comparison between risperidone, Olanzapine and placebo arms, reflected upon the same in their findings. Upon examining the NPI scores for subset of patients exhibiting moderate to severe agitation the Olanzapine treatment was found to have significant improvement with respect to risperidone. However, no significant improvement was observed in comparison to the placebo group.

The clinical benefits of another atypical antipsychotic, Aripiprazole, were assessed by Mintzer., *et al*. [34] in a double-blind, multicenter study. The study results reported the efficacy of Aripiprazole in providing relief from psychosis, with most significant improvements at a dosage of 10mg/day. Besides improvement in psychosis, 10 mg/day dosage was also found to be successful in providing relief from suspicious and hallucinatory behavior, and agitation. The various randomized, placebo-controlled trials of antipsychotics have provided results that show these drugs to be effective on patients with dementia and Alzheimer's disease. However, the trials have also provided insight that these drugs have positive effects with significant benefits on aggression and BPSD for a period of 6 - 12 weeks, after which the benefits do not remain significant as compared to placebo. The trials have also shed light that these antipsychotics provide benefit to patients at low doses, and high doses are not significantly beneficial, rather lead to increased risk of side effects and adverse events, including cerebrovascular events [26].

Risks Presented by Typical and Atypical Design

The use of antipsychotics agents in dementia patients, whether typical or atypical, have been associated with the occurrence of adverse events, which in many cases, offsets the benefits provided by these drugs. The first time the risks of antipsychotics, while being prescribed to treat BPSDs, was seen by the Canadian Health Regulatory Agency in 2002 [9]. The agency was concerned about the association of an antipsychotic, risperidone, with cerebrovascular adverse events (CVAEs). The adverse event was seen in elderly patients' clinical trials, and other agencies such as Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) have also had their concerns. FDA had also published warnings and instructed for the change of prescribing information for risperidone [35], while EMEA issued a public advisory related to the increased risk of CVAEs as well as mortality when being prescribed with antipsychotics [10]. Additionally, the UK's Committee on Safety of Medicines (CSM) also advised against the use of risperidone and Olanzapine for the treatment of BPSD as there was evidence relating to increased risk of strokes [7].

The cerebrovascular adverse events have been shown to pose a twofold risk in elderly patients being administered conventional and atypical antipsychotics [36]. The studies have shown the occurrence of such events to be higher in users of atypical antipsychotics than the non-users, even resulting in mortality [37,38]. The typical antipsychotics have also been shown to exhibit equally or even powerful cerebrovascular adverse events [39,40]. However, the conclusions pertaining to the adverse events for conventional drugs could only be drawn from prospective, and cohort studies, due to a lack of randomized control trials for the same. All the studies included in the systematic review reported the occurrence of extrapyramidal side effects, and serious adverse events such as cerebrovascular adverse events.

Deberdt., *et al*. [33] in their study reported the occurrence adverse cerebrovascular events in 2.5% of Olanzapine population, 2% of risperidone population, whereas no such events were observed in patients being administered placebo. As opposed to higher occurrence adverse cerebrovascular events in Olanzapine, the extrapyramidal side effects showed higher incidences with risperidone. With respect to the incidence of serious adverse events Brodaty., *et al*. [15] reported the occurrence of the same in at least 1 patient in each of the placebo and risperidone treatment groups. Also, 15 patients in the placebo group, and 28 patients in risperidone group suffered from life threatening events, whereas only 6 patients in the risperidone treatment arm were found to exhibit cerebrovascular adverse events. Out of the patients treated in risperidone group, 6 patients suffered from cerebrovascular events, in which 5 suffered from stroke and 1 suffered from a transient ischemic attack (TIA).

Four patients from the risperidone arm and 1 patient from the placebo arm suffered from cerebrovascular events in the trials conducted by Mintzer., *et al* [23]. Out of 4 patients, 1 suffered from stroke and 3 suffered from transient ischemic attack, whereas the placebo patient suffered from stroke. Other side effects included somnolence, UTI, hematoma, fall and injury and agitation. 2 patients also died from the risperidone group, while there were no deaths reported from the placebo arm of the clinical trial. Thus, this study was also not able to provide any positive evidence for risperidone against the potential risks it provided in comparison to the benefits.

Schneider, Dagerman, and Insel [4] conducted a study to assess the advantages and risks of antipsychotic use in dementia patients of the age of around 77 years. The randomized control trial assessed male and female patients of dementia and Alzheimer's disease on risperidone, Olanzapine, and Quetiapine as compared to placebo. The results of the trial aimed at assessing the time of discontinuation to understand the level of tolerability patients had for antipsychotics. The time of discontinuation showed no significant differences among the three antipsychotics tested (5.3 weeks Quetiapine, 8.1 weeks Olanzapine). In terms of severe adverse events, 2 patients from risperidone group suffered from cerebrovascular events and ischemic attack, and 1 from each other group suffered the same. In terms of death, 3 patients each from Quetiapine and placebo group died and 1 patient each died in the risperidone and Olanzapine group. In terms of moderate adverse events, the study noted gait disturbance, sedation, somnolence, headaches, extrapyramidal symptoms, depression, and fatigue, among others in all arms of the clinical trial. The study thus concluded that there were no significant advantages of antipsychotics over placebo in terms of risk vs. benefits, and that the use of antipsychotics did not significantly improve the quality of life of dementia patients as compared to patients who were on placebo.

Mintzer., *et al*. [34] reported the occurrence of cerebrovascular with respect to different dosages of Aripiprazole, and the highest dosage of drug (10 mg/day) was found to be associated with highest incidences of cerebrovascular adverse events (n = 4). At a dose of 2 mg/day, 1 incidence and 5 mg/day, 2 incidences of adverse events including cerebrovascular accident, cerebral ischemia, intra-cerebral hemorrhage and facial paralysis were observed. Tariot., *et al*. [28] conducted clinical trial to assess the relative efficacy, safety, and tolerability of Quetiapine, haloperidol and placebo arms. The rate of accidental injuries was found to be highest and similar in all the three treatment arms (41% - 46%), whereas somnolence occurred at the highest rate in haloperidol (36.2%). The serious adverse events were observed in all the three arms (10 Quetiapine; 15 haloperidol; 12 Placebo), with highest incidences in haloperidol. Also, 4 patients suffered non-serious cerebrovascular events (2 Quetiapine; 1 Haloperidol, 1 Placebo).

Mortality Caused by Antipsychotic Treatment

The antipsychotics are mainly prescribed for schizophrenia and bipolar disorder, but these drugs are also widely used off-label for treating BPSD in elderly patients suffering from Dementia [11]. However in 2005, the FDA, on the basis of 17 randomized controlled trials assessed that the adverse events associated with these drugs far outweighed the benefits in dementia patients, and the drugs also posed great risk on mortality when compared with placebo [41]. The agency thus asked the manufacturers of antipsychotics to add a 'black box' warning with the prescribing information so that the patients were adequately warned [13]. The Dementia Antipsychotic Withdrawal trial (DART-AD) conducted by Ballard., *et al*. [42] compared the adverse events related to typical (Thioridazine, Chlorpromazine, Haloperidol, Trifluoperazine) and atypical (Risperidone) antipsychotics in terms of mortality assessment.

The results of the trial showed a reduction in the survival rate in the group of patients receiving antipsychotic treatment as compared to the placebo group. The probability of survival in the antipsychotic treatment arm at the end of 12 month period was 70%, while the placebo group showed 77% of survival probability. The study also assessed the Kaplan-Meier estimates of mortality, which indicated that the subjects receiving active treatment (Hazard ratio = 0.58) suffered from significantly high risk of mortality as compared to those allocated to placebo. The researchers attributed cerebrovascular adverse events to be the probable cause of deaths. However, this claim could not be validated as the sample was very small and the cause of death on the death certificate is disputable. Also, none of the two types of antipsychotic exhibited significant difference in mortality rates, indicating the lack of ability of any particular class in reducing the incidences of mortality among patients with dementia and Alzheimer's disease.

Deberdt., *et al*. [33] in their trial recorded a higher rate of mortality in patients receiving olanzapine (2.9%), followed by those receiving risperidone (2%). The patients not receiving any active treatment (placebo) were found to have the minimal rate mortality, that is, 1.1%. The researchers reported the factors of age > 80 years, sedation, simultaneous use of benzodiazepine, and preexisting pulmonary conditions such as pneumonia increasing patient's susceptibility to mortality. Brodaty., *et al*. [15] reported 10 mortality events, with 4 death in the placebo groups and 6 in the risperidone group. They also reported pneumonia to be the most frequent cause of death, followed by the stroke in the risperidone group. However, the deaths could not be associated with drug with complete certainty.

Mintzer., *et al*. (2006) reported 3.8% mortality rate in the risperidone group, and 2.5% in placebo group, with deaths occurring during or 30 days post the cessation of the trial. The causes of deaths were cardiac arrests (2), sudden death (1), cerebrovascular accident (1), aggravated dementia (2), myocardial infarction (1) and congestive heart failure (2) in the patients receiving active treatment whereas the patients receiving place died due to pneumonia (3), sudden death (1), myocardial infarction (1) and arteriosclerosis (1). The dose dependent mortality events were recorded by Mintzer., *et al*. [34] where the high dosage of aripiprazole drug resulted in highest number of deaths (8). The dosage of 5 mg/day had comparable mortality incidents with respect to placebo. Tariot., *et al*. [28] also reported the occurrence of mortality events only in the patients administered the typical antipsychotic haloperidol (2). Thus, the information form the various randomized controlled trials have indicated towards the occurrence of mortality events, with higher incidences associated with active treatment arms.

Conclusions and Discussions

The study assessed 8 randomized controlled trials of various typical and atypical antipsychotics on patients with dementia, Alzheimer's disease, vascular dementia and mixed dementia. The trials mainly enrolled elderly people with the mean age ranging from 77 to 83, and the majority of them were females. The results of various trials reported the efficacy, tolerability, and safety of these drugs. The majority of the trials found out that low doses of typical or atypical antipsychotics were helpful in maintaining the behavioral and psychotic symptoms of the elderly, with increased doses being insignificant when compared to placebo. The studies also found out that there was no significant difference between typical and atypical antipsychotics in treating the disease, and that the increased doses of these antipsychotics significantly increased side effects. Many studies included side effects related to cerebrovascular events, as well as ischemic stroke. Some of the adverse events were very serious, leading to mortality. Other adverse events included somnolence, gait disturbance, and agitation. This review study thus, concludes that no significant efficacy measures were seen by special administration of either typical or atypical antipsychotics. The increased administration of high doses of antipsychotics also led to severe to moderate side effects, as compared to placebo. There is a need to assess the efficacy of these antipsychotics in a vast population sample for a longer duration to realize the actual efficacy and tolerability of these drugs.

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