

Research Article

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The Effects of Seroquel on Agitation and Cognition in Alzheimer's Patients: A Limited Integrative Literature Review



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Abstract

Background: Alzheimer's disease is a progressive, irreversible disease that effects over 5 million Americans and costs the United States over \$200 billion a year, with no known cure. Side effects can be experienced throughout the disease process, to include agitation, delusions, hallucinations, aggression, memory loss, and many more. This can severely influence both the family's and the patient's quality of life.

Objectives: This limited integrative literature review explores the use of Seroquel (quetiapine), an atypical antipsychotic medication, on Alzheimer's patients with cognitive and/or behavioral disturbances.

Methodology: A comprehensive search strategy was used to search the current literature on the effects of Seroquel (quetiapine) on this patient population. Seven articles were reviewed and chosen for use in this literature review, and their evidence is presented in Table 1 at the conclusion of this paper.

Results: Varying results were found, with the majority of patients tolerating the Seroquel (quetiapine) very well. A reduction in extrapyramidal symptoms were also seen with the use of this particular medication, as compared with other atypical antipsychotics. The main limitation of these studies is a small sample size.

Conclusion and Recommendation: Future research is needed on this subject, preferably using larger sample sizes, in order to find supporting evidence for the use of Seroquel (quetiapine) with Alzheimer's patients.

Keywords: Agitation; Alzheimer's; Cognitive disturbances; Literature review; Quetiapine, Seroquel

Introduction

Alzheimer's disease is a progressive, irreversible type of dementia that effects approximately 5.4 million Americans and is the fifth leading cause of death for people over the age of 65 [1]. The total payment for 2016 for dementia care was estimated to be \$236 billion [1]. Unfortunately, there are currently no known preventions or cures for Alzheimer's dementia. This disease can detrimentally affect both the patient and the family or caregivers caring for the patient.

The cognitive and behavioral changes that occur throughout the disease process can be very stressful to all who are involved. In the beginning stages, the patient may exhibit symptoms such as irritability, anxiety, and depression [2]. In the later stages, symptoms such as agitation, aggression, hallucinations, and delusions can occur. This literature review focuses on the later stages of Alzheimer's, including cognitive decline (i.e. memory loss, word recall, and delusions) and agitation, as they appear

to be the most prevalent and difficult symptoms to manage as the disease destroys brain function [1]. Although there are many interventions that may temporarily subside these symptoms, Alzheimer's patients often times need pharmacological interventions when symptoms become severe and/or persist despite non-pharmacological attempts [2].

Atypical antipsychotics, such as Seroquel (quetiapine), have not been approved by the U.S. Food and Drug Administration (FDA) for use in Alzheimer's patients with cognitive and behavioral disturbances, because they can potentially worsen those same cognitive and behavioral disturbances [2]. The Alzheimer's Association [2] urges caution when trying to choose the proper medication for an off-label use, such as Seroquel (quetiapine). The two types of medications that have been approved by the FDA to treat cognitive symptoms of Alzheimer's disease are cholinesterase inhibitors, such as Aricept, Exelon

and Razadyne, and Namenda (memantine) [2]. More research is needed to either support or refute the off-label use of these medications. The purpose of this paper is to evaluate how Seroquel (quetiapine) effects agitation and cognition in Alzheimer's patients.

Methods

An ultimate database search of CINAHL, Cochrane Database of Systematic Reviews, and MEDLINE was performed. Search terms included "Alzheimer", "Seroquel/quetiapine", and "agit*". The use of the asterisk for the term agitation allowed for the search to include every word beginning with that prefix. These search terms also resulted in articles about both agitation and cognition of Alzheimer's patients taking Seroquel.

Articles were included if the majority of the research subjects were diagnosed with Alzheimer's disease. The subjects were being administered Seroquel/quetiapine, and the outcomes being measured included both/either symptoms of agitation and/or cognitive effects, such as psychosis and/or altered mental status/confusion. Exclusion criteria included articles addressing other medications and articles discussing dementia without specifying Alzheimer's disease. Articles included both inpatient and outpatient participants to prevent substantial limitation of data. Level and quality of evidence was determined by using the strength of evidence pyramid [3]. All articles used were quantitative studies of randomized controlled trials and/or evidence summaries.

Results

Search Results

Two hundred and ninety-six articles resulted in the initial Medline search using "Alz*" and "Agita*" as search terms, followed by one hundred and sixty-six with the addition of the search term "Med*". Upon reviewing the titles and abstracts, many of the studies addressed patients with dementia, but not specifically patients with Alzheimer's disease. There were also many studies comparing the use of antipsychotics other than Seroquel (quetiapine). Due to the majority of these articles not fully addressing every aspect of the research question, this initial search was discarded.

A subsequent search was performed, comparing Seroquel (quetiapine) to Haldol (haloperidol), resulting in thirty-three, fifty-eight, and sixty-seven articles from Medline, Cochrane database of systematic reviews, and CINAHL respectively. Five of these articles were initially chosen, since they addressed patients with Alzheimer's disease with the two anti-psychotic medications. However, the dependent variables of both agitation and cognition were not sufficiently addressed, resulting in a final revision of the research question to solely include Seroquel (quetiapine) as the independent variable.

A final search resulted in twenty-eight articles from Medline, Cochrane database of systematic reviews, and CINAHL using the

search terms "Alz*", "Seroquel" OR "quetiapine", and "agit*". After careful review of all twenty-eight articles' titles and abstracts, fifteen articles were selected for full-text review. The remaining thirteen articles were discarded, because they did not fully address the research question. Ultimately, seven articles were chosen for use in this limited integrative literature review addressing the use of Seroquel (quetiapine) for both agitation and cognition signs and symptoms in Alzheimer's patients. Four of the seven studies were level 2 randomized controlled trials, with one retrospective naturalistic study, and one level 4 and level 6 study. Given the limited nature of this integrated literature review, it was found to be educational in nature, despite the overwhelming evidence against the use of Seroquel (quetiapine) in Alzheimer's patients.

A summary of the seven included studies' design/method/ level of evidence, sample/setting, major variables studied and their definitions, interventions, measurements, data analysis and results, and an appraisal of worth to practice can be found in Table 1 in the appendix. The articles are organized alphabetically by the first author's last name. The data analysis and results sections are color-coded to assist in the finding of the two dependent variables being studied: agitation and cognition.

Effects of Seroquel (quetiapine) on Agitation

Six of the seven studies addressed the effects of Seroquel (quetiapine) on agitation with Alzheimer's patients (Table 1) [4-9]. They all assessed agitation levels using the Cohen-Mansfield agitation inventory (CMAI), the Neuropsychiatric Inventory (NPI), and/or the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Overall, Seroquel (quetiapine) showed to be well-tolerated in this patient population and decreased clinical signs and symptoms of agitation, such as irritability and aggression. This is evidenced by lower CMAI, NPI and BEHAVE-AD scores when compared to baseline. Ballard et al. [4] presented one exception to these findings; there were no significant differences seen in agitation levels between groups. All participants in the Ballard et al. [4] study showed improved scores from baseline, regardless of being in the control or intervention group.

Deyn, Eriksson, and Svensson [5], Fujikawa et al. [6], Onor, Saina, and Aguglia [7], Rocca et al. [8], and Savaskan et al. [9] all discussed Alzheimer's patients as having cognitive stability while taking Seroquel (quetiapine) and that the study participants tolerated the medication well. Fujikawa et al. [6] specifically discussed the decrease in occurrence of extrapyramidal symptoms with the use of Seroquel (quetiapine) compared to other antipsychotics. Onor, Saina, and Aguglia [7] showed decent efficacy of Seroquel (quetiapine) in reducing psychotic symptoms and decreasing the risk of iatrogenic parkinsonism and tardive dyskinesia in elderly patients. Savaskan et al. [9] recommended that Seroquel (quetiapine) be started at the lowest possible dose and increased slowly in order to avoid side effects, even though it is generally well tolerated.

Table 1: Evidence Table

Citation	Design/ Method Level of Evidence	Sample/ Setting	Major Variables Studied and their Definitions	Intervention	Measurement	Data Analysis and Results	Appraisal: Worth to Practice
BallardC, Margallo- LanaM, Juszczak E, Douglas S, Swann, et al. [4]. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: Randomised double blind placebo controlled trial. BMJ, 1-5.	Randomized, double- blind, placebo, controlled trial (RCT)	Setting: Facilities located in the north-east of England (Newcastle) Sample: 93 Alzheimer's disease/ demented patients with clinically significant agitation 25 patients were assigned to the rivastigmine group, 26 to the quetiapine group, and 29 placebo (13 withdrew consent or died).	Independent variable: Seroquel (quetiapine) -This medication is an atypical antipsychotic being trialed with Alzheimer's patients to control their signs and symptoms of agitation and cognitive changes, such as hallucinations. Dependent variables: Agitation and cognition -Agitation was defined as a score above 39 on the Cohen- Mansfield agitation inventory (see measurement column for more details) -Cognition was defined as the change in abilities to complete simple tasks when completing the severe impairment battery (areas consist of attention, orientation, language, memory, visuo-spatial ability, and construction) -The SIB consists of 40 items, or simple one-step commands. -Scores range from 0-100, and a score of less than 63 is considered “very severely impaired”	This study consisted of 3 intervention groups using atypical antipsychotics (quetiapine and rivastigmine) and placebo - “The study statistician randomly assigned patients in equal numbers to active quetiapine plus placebo rivastigmine; placebo quetiapine plus active rivastigmine; or placebo rivastigmine plus placebo quetiapine (double dummy). - Doses of 25-50mg quetiapine twice daily and 3-6 mg rivastigmine twice daily by week 12 and 50mg quetiapine twice daily or ≥ 9 mg rivastigmine daily between week 12 and week 36 were aimed for.	The Cohen-Mansfield agitation inventory was used (total score exceeding 39) -Consists of 29 items that measure the frequency of physically aggressive behaviors (such as hitting or kicking), physically non- aggressive behaviors (such as pacing or restlessness), and verbally agitated behaviors (such as screaming or cursing). Participants were evaluated again after 6 and 26 weeks. An additional severe impairment battery was performed after 12 weeks. Outcomes measured using a standardized evaluation of agitation, using the severe impairment battery, to measure cognitive change in people with severe dementia. Effects measured using the agitation inventory assessment and the severe impairment battery. Agitation was measured with the agitation inventory and cognition was measured with the severe impairment battery. General assessments included ECGs, blood work, and functional assessment staging.	ANOVA compared pairs of treatment groups; mean differences between groups were adjusted for baseline values. Results: -No significant differences were found between groups for the agitation inventory, but individual groups showed improvements from baseline to six weeks post- treatment. -Patients in the quetiapine group had an estimated mean difference in change in severe impairment battery (SIB) score from baseline of -14.6 points, with a 95% confidence interval and a p-value of 0.0009 (a significantly greater deterioration cognitively). -Significant changes were seen with Seroquel (quetiapine) compared to the placebo group for the SIB from baseline (-14.6 at week 6 with a p-value of 0.009; -15.4 at week 26 with a p-value of 0.01)	Overall, quetiapine was shown to have no significant improvements in dementia patients for agitation and showed an association with greater cognitive decline. This shows a practical clinical application, in that dementia patients should not be given antipsychotics for agitation. Limitations include multiple evaluations, a modest sample size, lack of evidence of efficacy, and patients unable to complete the SIB. Despite the limitations, the effect of quetiapine on cognition is still important.

<p>Deyn P P, Eriksson H, Svensson H [5] Tolerability of extended-release quetiapine fumarate compared with immediate-release quetiapine fumarate in older patients with Alzheimer's disease with symptoms of psychosis and/or agitation: A randomized, double-blind, parallel-group study. International Journal of Geriatric Psychiatry 27: 296-304</p>	<p>Randomised, double-blind, double-dummy, parallel-group, controlled Phase III study (RCT)</p> <p>Level 2</p>	<p>Sample: 100 Alzheimer's disease patients, greater than or equal to 65 years of age, with symptoms of psychosis and/or agitation, requiring antipsychotic medication.</p> <p>68 were randomly assigned to the quetiapine XR group and 32 to the quetiapine IR group (a 2:1 ratio).</p> <p>Setting: Nursing homes in five countries (Australia, Belgium, Canada, Norway, and South Africa)</p>	<p>Independent variable: Seroquel (quetiapine) extended-release and immediate-release</p> <p>Dependent variable: Incidence and adverse events, efficacy and other safety assessments.</p> <p>Note: For the purpose of this paper, I will be looking at the secondary efficacy variables of change in baseline in the Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory (CMAI), Mini-Mental State Examination (MMSE) and Clinical Global Impression-Severity of Illness (CGI-S) scores.</p>	<p>The quetiapine XR group received a dose of 50 mg/day, and the IR group received 25 mg/day. Doses were increased to 100 mg/day by day 4 (fixed-dose titration period)</p> <p>At day 8, a flexible dose period began of 50-300 mg/day.</p> <p>Baseline measurements and change from baseline measurements were taken at day 42 (NPI, CMAI, MMSE, and CGI-S scores).</p>	<p>Scores were obtained at baseline and at 42 days to see a change from baseline in the following scores: NPI, CMAI, MMSE, and CGI-S.</p> <p>Means and standard deviations were calculated, presented in Table 4 on page 302.</p>	<p>Note: No specific statistical testing was mentioned. No p-values were given.</p> <p>For the quetiapine XR group:</p> <ul style="list-style-type: none"> -NPI scores improved from baseline with a mean of -20.0 and a standard deviation of 26.4 -CMAI scores improved with a mean of -14.0 and SD of 18.1 -MMSE scores slightly changed with a mean of -0.4 and SD of 3.2 -CGI-S scores changed with a mean of 20 and SD of 29.9 <p>For the quetiapine IR group:</p> <ul style="list-style-type: none"> -NPI scores improved from baseline with a mean of -25.0 and SD of 16.7 -CMAI scores improved with a mean of -16.1 and SD of 12.5 -MMSE scores changed with a mean of 0.0 and SD of 2.98 -CGI-S scores changed with a mean of -1.3 and SD of 1.5 <p>Steady patterns of improvement were seen in NPI scores for both groups.</p> <p>Progressive improvements were seen in CMAI and CGI-S scores.</p> <p>There was no deterioration of cognition in either group (MMSE scores).</p>	<p>Quetiapine is not currently approved for the use of psychosis and/or agitation in Alzheimer's patients. This study showed improvements in NPI scores for both treatment groups, as well as progressive improvements in CMAI and CGI-S scores. This indicates some improvement in the symptoms of psychosis and agitation, without a significant change in cognition (as measured by the MMSE). Note: This study also notes that quetiapine was generally well tolerated among this patient population. Limitations include a short-term design, small sample size, no placebo control group, and a lack of formal statistical consideration.</p>
<p>Fujikawa T, Takahashi T, Kinoshita A, Kajiyama</p>	<p>8 week open study</p> <p>Level 4</p>	<p>Sample: 16 patients (2 men and 14 women) with</p>	<p>Independent variable: Seroquel (quetiapine)</p>	<p>Quetiapine (25-200 mg/day) was prescribed</p>	<p>Behavioral and psychological symptoms of dementia</p>	<p>Wilcoxon signed rank test used Data reported as means \pm SD P-value of <0.01</p>	<p>This article's data indicates that quetiapine is</p>

<p>H, Kurata A. Yamashita H, [6] Quetiapine treatment for behavioral and psychological symptoms in patients with senile dementia of Alzheimer type. <i>Neuropsychobiology</i> 49: 201-204.</p>		<p>senile dementia of Alzheimer type (SDAT) Setting: Participants were recruited through the inpatient (6 patients) or outpatient (10 patients) units of the Department of Psychiatry, National Sanatorium Kamo Hospital, Hiroshima, Japan.</p>	<p>Dependent variable: BEHAVE-AD and CMAI scores (measuring changes in agitation and cognition)</p>	<p>bed for 8 weeks. -25-75 mg/day for the first week -dosage could be stepped up to 200 mg/day, adjusting as needed each week.</p>	<p>(BPSD) were evaluated with the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and Cohen-Mansfield Agitation Inventory (CMAI) at baseline and week 8.</p>	<p>used for significance. Quetiapine doses at baseline were a mean of 45.3 ± 19.7 mg. Quetiapine doses at 8 weeks were 76.6 ± 51.9 mg. Significant improvements were seen in delusions (baseline: 4.50 ± 3.91; endpoint: 1.44 ± 1.66; $p=0.0033$) and aggressiveness (baseline: 4.19 ± 3.26; endpoint: 1.56 ± 1.80; $p=0.0020$). A significant decrease was seen in CMAI total scores (baseline: 64.69 ± 20.09; endpoint: 40.63 ± 8.57; $p=0.0007$).</p>	<p>effective in controlling BPSD without many adverse events. The authors stated that quetiapine is also associated with less frequent occurrence of EPS. Main limitation is the small sample size.</p>
<p>Onor M L, Saina M, Aguglia E [7] Efficacy and tolerability of quetiapine in the treatment of behavioral and psychological symptoms of dementia.</p>	<p>Descriptive study Level 6</p>	<p>Sample: 41 patients, aged 60-85 years, with a diagnosis of dementia and psychotic symptoms. -20 patients with Alzheimer's</p>	<p>Independent variable: Seroquel (quetiapine) starting at 12.5 mg/day and increasing every 3 days until a reduction in psychotic symptoms is seen. Dependent variables: NPI and BEHAVE-AD scores measuring the response to</p>	<p>Seroquel (quetiapine) was started at 12.5 mg/day at bedtime for all participants and increased every 3 days until a</p>	<p>NPI and BEHAVE-AD scores were taken at baseline, 4 weeks and 12 weeks. Comparison of changes over time were reported</p>	<p>Paired t tests and analysis of variance were used. Statistically significant score reductions were seen at week 4 in most of the NPI scores with a p-value $< .01$. Changes were also observed in the BEHAVE-AD scores. Mean NPI scores at baseline, 4</p>	<p>This study showed a decent efficacy of quetiapine in reducing psychotic symptoms in dementia patients. It was noted that quetiapine</p>
<p>American Journal of Alzheimer's Disease & Other Dementias 21(6): 448-453</p>		<p>disease -6 with mixed dementia -5 with Lewy body dementia -4 with Parkinson's disease Setting: Alzheimer Evaluation Unit (Trieste-Unita Clinica Operativa of Clinical Psychoiatry, University of Trieste)</p>	<p>treatment at baseline, 4 weeks, and 12 weeks.</p>	<p>reduction in psychotic symptoms is seen (initially increased to 25 mg in 2 divided doses, morning and evening, and then increased by 25 mg every 3 days).</p>		<p>weeks and 12 weeks: <ul style="list-style-type: none"> • Delusions: -Baseline: 5.56 ± 4.48 -4 weeks: 2.28 ± 2.46 ($p<.01$) -12 weeks: 1.38 ± 2.43 ($p<.05$) • Hallucinations: -Baseline: 3.00 ± 3.88 -4 weeks: 1.15 ± 1.56 ($p<.01$) -12 weeks: 0.51 ± 0.88 ($p<.05$) </p>	<p>(atypical antipsychotic agent) has a reduced risk of iatrogenic parkinsonism and tardive dyskinesia in elderly patients.</p>

						<ul style="list-style-type: none"> • Hallucinations: <ul style="list-style-type: none"> -Baseline: 3.00 ± 3.88 -4 weeks: 1.15 ± 1.56 (p<.01) -12 weeks: 0.51 ± 0.88 (p<.05) • Agitation/Aggressiveness: <ul style="list-style-type: none"> -Baseline: 6.12 ± 3.27 -4 weeks: 2.59 ± 1.64 (p<.01) -12 weeks: 1.09 ± 1.32 (p<.01) • Euphoria: <ul style="list-style-type: none"> -Baseline: 0.53 ± 1.19 -4 weeks: 0.18 ± 0.39 (p<.05) • Disinhibition: <ul style="list-style-type: none"> -Baseline: 1.09 ± 2.17 -4 weeks: 0.43 ± 1.07 (p<.05) • Irritability: <ul style="list-style-type: none"> -Baseline: 3.25 ± 2.66 -4 weeks: 1.28 ± 1.27 (p<.01) -12 weeks: 0.54 ± 0.62 (p<.01) • Mean BEHAVE-AD scores at baseline, 4 weeks and 12 weeks • Paranoid and delusional ideation: <ul style="list-style-type: none"> -Baseline: 4.54 ± 4.81 -4 weeks: 2.64 ± 3.22 (p<.001) -12 weeks: 0.85 ± 1.62 (p<.001) • Hallucinations: <ul style="list-style-type: none"> -4 weeks: 0.93 ± 1.78 -12 weeks: 0.28 ± 0.65 (p<.05) -12 weeks: 1.63 (p<.001) -12 weeks: 0.82 ± 1.46 (p<.01) -4 weeks: 1.93 ± 	<p>Quetiapine showed to be tolerated well and reduced behavioral symptoms of delusions, hallucinations and aggressiveness.</p> <p>Reduced stress of caregivers was also noted, which decreases the costs of institutionalization and helps the families better manage the patient at home.</p> <p>Limitations include: open-label trial on a small sample size (lack of standard features of clinical trials such as placebo controls, randomization, and blinding of raters), varying doses of quetiapine to produce clinical improvement, and short duration of the trial.</p>
Rocca P, Marino F, Montemagni C, Perrone D, Bogetto F [8]	Retrospective naturalistic study	Sample: 58 outpatients (36 women and 22 men) with a DSM-IV TR diagnosis	Independent variable: Quetiapine	6-month treatment of quetiapine (20 patient patients were treated	2 trained psychiatrists performed cognitive, functional, and psychiatric-behavioral tests	Univariate ANOVA for changes in continuous outcome measures.	Consistent and clinically significant improvements were seen on behavioral

<p>Risperidone, olanzapine and quetiapine in the treatment of behavioral and psychological symptoms in patients with</p>	<p>Dependent</p>	<p>Sample: 58 outpatients (36 women and 22 men) with a DSM-IV-TR diagnosis of Alzheimer's disease with behavioral disturbances Setting: Outpatients at the Alzheimer Evaluation Unit (Department of Neuroscience, Turin, Italy)</p>	<p>Dependent variables: NPI and MMSE scores</p>	<p>with quetiapine)</p>	<p>(collected through chart review). MMSE measured cognitive function. NPI investigated psychiatric and behavioral diseases. Behavioral symptoms at baseline were a mean NPI score >25.</p>	<p>Pearson correlations for baseline MMSE score with changes in NPI scores. Significance level was set at $p<0.05$ (two-tailed test). Means and standard deviations were reported at baseline and end-points. The mean total NPI score fell 33.3% from baseline in the quetiapine group, a significant reduction (baseline 25.20 \pm 7.85, end-point 16.80 \pm 7.88). There were also significant reductions in delusions (baseline 3.60 \pm 2.30, end-point 1.50 \pm 1.61), hallucinations (baseline 2.20 \pm 2.09, end-point 0.90 \pm 1.62), and agitation/aggression (baseline 3.40 \pm 1.67, end-point 2.80 \pm 1.58). No significant changes were seen in MMSE scores (baseline 19.33 \pm 4.14, end-point 21.26 \pm 5.45). Baseline cognitive function (MMSE) was significantly correlated with decreased NPI scores ($r=0.373$, $p<0.004$), agitation ($r=-0.293$, $p<0.025$), and delusions ($r=0.246$, $p<0.062$).</p>	<p>disturbances of delusions, hallucinations and agitation. Cognitive function remained stable. This study's results falls in line with results from other trials and RCTs. Limitations include those inherent to observational studies, lack of control group, non-blinded and non-randomized, patients taking concomitant medications (possible combined effect), and small sample size.</p>
<p>Savaskan E, Schnitzler C, Schroder C, Cajochen C, Muller-Spahn F [9] Treatment of behavioural,</p>	<p>Comparative, randomized, open-label trial Level 2</p>	<p>Sample: 30 patients with Alzheimer's disease, 22 of which completed the study (11 in the</p>	<p>Independent variable: Seroquel (quetiapine) Dependent variables: behavioral</p>	<p>Patients received quetiapine 25-200 mg -initial dose of 25 mg</p>	<p>Patients received test batteries at baseline (visit one) and at the end of the 5 week trial (visit 3).</p>	<p>Analysis of variance was used to analyze changes over time, followed by Duncan's</p>	<p>Compared with other antipsychotic medications, quetiapine</p>

		<p>quetiapine group) The quetiapine group consisted of 9 females and 2 males. Setting: In-patients hospitalized on the geronto-psychiatric ward</p>	<p>(NPI and NOSGER scores) and cognitive (MMSE and CERAD scores) disturbances</p>	<p>-dose increased weekly by 25 mg</p>	<p>The NPI interview was used to assess behavioral disturbances, including delusions, hallucinations, agitation/aggression, disinhibition, and irritability. The CERAD battery included many assessments (MMSE included).</p>	<p>multiple-range tests when the ANOVA was significant. Quetiapine reduced delusions ($p=0.017$) and agitation ($p=0.016$) and improved word recall ($p=0.031$) and word list memory ($p=0.006$). Mean baseline MMSE 19.9 \pm 1.3 for the quetiapine group with a mean ending dose of 125 mg. No significant changes were noted in MMSE scores.</p> <p>Note: Table 1 on page 509 lists every individual patients and their results at baseline and 5 weeks.</p>	<p>has shown to be effective in treating behavioral disturbances in Alzheimer's patients at moderate doses. Quetiapine has shown to have stable cognitive effects, which improves patients' functionality (measured through ADLs). In order to avoid side effects, it is recommended that quetiapine be started at very low doses and be increased slowly. Main limitation is the small sample size.</p>
Vigen C L P, Mack W J, Keefe R S E, Sano M [10] Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: Outcomes from CATIE-AD. American Journal of Psychiatry 168(8): 831-839.	RCT Level 2	<p>Sample: 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior Setting: Ambulatory outpatients living at home or in an assisted living facility; 42 study sites.</p>	<p>Independent variable: Quetiapine Dependent variable: cognitive function (several measures). -the MMSE -the cognitive subscale of the Alzheimer's Disease Assessment Scale -3 additional ADAS subscales (concentration/distractibility, number cancellation, and executive function) -tests of category instances -the finger tapping test, preferred and nonpreferred hand -the Trail Making Test, Part A -a measure of working memory deficit</p>	<p>Patients were randomly assigned, in a double-blind fashion, to receive quetiapine, a placebo, or one of two other atypical antipsychotics over a 36 week trial period.</p>	<p>Cognitive assessments were performed by clinicians at baseline, 12 weeks, 24 weeks, and 36 weeks. Scores were obtained for the MMSE, the cognitive subscale of the Alzheimer's Disease Assessment Scale, and the Brief Psychiatric Rating Scale</p>	<p>Normalized z scores t tests ANOVA Linear regression models Participants significantly declined on several measures of cognitive function. The average decline on the MMSE score was 2.46 points greater than the placebo group ($p=0.004$). Weekly rate of change for quetiapine group compared to placebo: -Brief Psychiatric Rating Scale, cognitive factor: 0.036 ($p=0.05$) Weekly rate of change in total sample: - MMSE -0.067 ($p<0.001$) - Brief Psychiatric Rating Scale</p>	<p>This study showed cognitive decline in patients taking atypical antipsychotics like quetiapine, with no significant differences between drugs. These results are consistent with results of meta-analyses with larger sample sizes such as this study. Clinically speaking, these results are more generalizable compared to smaller sample sizes. No specific limitations were noted.</p>

					cognitive factor: 0.010 (p=0.003) Cognitive subscale of ADAS: 0.123 (p<0.001) Concentration/ distractibility: 0.006 (p=0.01) Cognitive summary: -0.011 (p<0.001) Note: All of these changes were not in the favorable direction	
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Seroquel (quetiapine) is currently not approved by the Food and Drug Administration (FDA) for use in Alzheimer's patients. In 2005, the FDA issued a black box warning on atypical antipsychotics, like Seroquel (quetiapine), because they were shown in some studies to increase the risk of death in elderly patients with dementia [5]. The increased level of mortality has created a great debate as a result of conflicting data from studies concerning the use of atypical antipsychotics. Ballard et al. [4] and Vigen et al. [10] showed evidence of adverse reactions to Seroquel (quetiapine) with Alzheimer's patients, along with other atypical antipsychotics like risperidone and olanzapine. It is important to note, though, that this evidence has come from studies with schizophrenia and other psychotic disorders, rather than patients with Alzheimer's dementia. Thus far, Seroquel (quetiapine) has shown to be favorable for Alzheimer's patients with agitation. Although the majority of articles discussed thus far contain small sample sizes, they were still able to achieve statistical and clinical significance levels (Table 1).

Effects of Seroquel (quetiapine) on Cognition

All seven studies addressed the effects of Seroquel (quetiapine) on cognition in patients with Alzheimer's disease [4-10]. The results of these studies are displayed in Table 1. The cognitive changes of study participants were measured using the Severe Impairment Battery (SIB), the Mini-Mental State Examination (MMSE), the Clinical Global Impression-Severity of Illness scale (CGI-S), and portions of the BEHAVE-AD scale. As previously mentioned, Ballard et al. [4] and Vigen et al. [10] showed a cognitive decline in patients taking atypical antipsychotics like Seroquel (quetiapine), whereas the other five studies showed stable cognitive function [5-9].

The variable of cognition was broken down into delusions, hallucinations, word recall, word list memory, euphoria, and disinhibition. Vigen et al. [10] summarized their findings as showing a cognitive decline in patients taking atypical antipsychotics, but they also commented that these results are consistent with results of meta-analyses with larger sample sizes. Without more specific and supporting results pertaining to the cognitive decline in patients, it is difficult to analyze if

these statistics are truly accurate or if the sample size was so large that it created significant results. Overall, a decrease in delusions and hallucinations and an increase in word recall and word list memory can be seen in these studies [4-10]. A positive change in cognition can be seen with decreased MMSE and SIB scores. Although Rocca et al. [8] reported no significant changes in MMSE scores, they did report that MMSE scores were significantly correlated with a decreased NPI score for agitation and delusions.

Limitations of the Evidence

One of the major limitations for this review is the lack of evidence supporting the use or disuse of Seroquel (quetiapine) for the treatment of agitation and/or cognitive function in Alzheimer's patients. There are many studies reviewing the effects on patients experiencing psychosis, but not patients with Alzheimer's disease. This subject has only recently become more studied, despite not being approved by the FDA for use in this patient population. It would be beneficial to have more clinical trials evaluating the use of Seroquel (quetiapine) on patients with Alzheimer's disease.

Six of the seven studies stated a limitation of a small sample size. Ballard et al. [4] reported a sample size of 93; Deyn, Eriksson, and Svensson [5] reported 100; Fujikawa et al. [6] reported 16; Onor, Saina, and Aguglia [7] reported 41; Rocca et al. [8] reported 58; Savaskan et al. [9] reported 30. Vigen et al. [10] did not report any study limitations and had the largest sample size of 421 participants, yet reported cognitive decline with the use of Seroquel (quetiapine). It is important to note that these moderate to large sample sizes are a potential limitation of valid study results. Without more research to support these findings, it is difficult to make that judgement call at this time.

Rocca et al. [8] reported limitations relative to the nature of observational studies, as there were no control groups, no randomization, and no blinding involved. The researchers were unable to control for other influencing variables, such as patients taking other medications that could create a combined effect with Seroquel (quetiapine). It is important to note, though, that

even observational studies can add a lot of clinical importance, and this study produced significant results that were in line with other studies and randomized controlled trials.

Two of the studies reported a limitation of having multiple comparisons or evaluations [4,7]. Onor and colleagues [7] compared different dosages of Seroquel (quetiapine), whereas Ballard and colleagues [4] compared multiple anti-psychotics and a placebo group. The greatest limitation for these studies that were not level 2 evidence or randomized controlled trials is that they lacked randomization, a control group, and the blinded fashion that eliminates certain biases.

Discussion

Two of the seven included studies showed a decline in cognitive function with the use of Seroquel (quetiapine) in Alzheimer's patients [4,10]. The other five included studies either showed a stable cognitive function or some improvement in scores for cognitive function and/or agitation [5-9]. Based on the majority of the included studies having small sample sizes and the variability in obtained results, there is not enough consistent data to support the use of Seroquel (quetiapine) in Alzheimer's patients for cognitive and/or behavioral problems. However, it is worth noting the clinical importance of the off-label use of Seroquel (quetiapine) within this patient population. Despite their limitations, many of the studies showed improvement in symptoms of psychosis and agitation without any changes in cognition [5-9].

Alzheimer's disease is a progressive disease that worsens over time as the brain slowly dies [1]. Given this definition, it is expected to see cognitive decline in patients with Alzheimer's as their disease progresses. Ballard et al. [4] and Vigen et al. [10] discuss this steady deterioration in mental status over time, and they believe Seroquel (quetiapine) hastens that process. On the other hand, there have been many other studies that have investigated the off-label use of atypical antipsychotics, such as Seroquel (quetiapine), that have shown time and again the efficacy of this drug for use in reducing the debilitating symptoms of dementia [6]. Research has shown that typical antipsychotics can cause severe side effects, such as iatrogenic parkinsonism and tardive dyskinesia, but Seroquel (quetiapine) does not have these effects [7].

Recommendations

Practice

The FDA has placed a black box warning label on atypical antipsychotics, such as Seroquel (quetiapine), for the use in Alzheimer's patients, as there is an increased risk for death [5]. However, Seroquel (quetiapine) has shown to be tolerated very well within this patient population, and is currently being used to manage cognitive and behavioral symptoms in Alzheimer's patients as an off-label use [5-9]. Based on the evidence provided in Table 1, it is noted that Seroquel (quetiapine) is well

tolerated but should be started at the lowest dose possible and then adjusted thereafter according to the patient's response to treatment.

Education

Nurses, physicians, and other healthcare professionals should be aware of the risks and possible side effects that Seroquel (quetiapine) could have on patients with Alzheimer's disease. They should also educate themselves on the disease process itself and try as many non-pharmacological interventions as possible before resorting to the use of atypical antipsychotics in this medically vulnerable population. The Alzheimer's Association [2] is a great resource that provides education to both the health profession and the general public in ways that are best understood.

Healthcare Policy

Alzheimer's disease is a global issue with no currently known causes or cures [1]. It is a progressive and irreversible disease. It costs the United States over \$200 billion a year, which is expected to climb as the incidence rises over time. Further research needs to be done to find and prevent the causes of Alzheimer's disease. Although Seroquel (quetiapine) does not treat the disease itself, it allows for the more psychotic disturbances to be at bay, ultimately improving the patients' quality of life, as evidenced by the research within this study (Table 1).

Future Research

Given what is currently known about atypical antipsychotics, such as Seroquel (quetiapine), for the use in Alzheimer's patients with behavioral and cognitive disturbances, more research needs to be done. Many of the other atypical antipsychotics, excluding Seroquel (quetiapine), have extrapyramidal effects on patients [6-7]. Most of the presented studies are single studies with small sample sizes. More randomized controlled trials need to be done on larger sample sizes in order to get accurate and generalizable results that are clinically and statistically significant. This patient population is extremely vulnerable to the side effects of medication due to polypharmacy. The FDA needs more supportive evidence in order to approve such medications for what is currently being used as off-label.

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