Efficacy of SSRIs for treating depression in Alzheimer's disease

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Abstract

Contrary to popular belief, memory loss and other cognitive abilities severe enough to interfere with daily life are not a normal part of aging. Worldwide, 50 million people are living with a degenerative brain disease known as dementia. [1] In the U.S., 5.7 million Americans are living with the most common form of dementia: Alzheimer's disease (AD).[1] AD is a type of dementia that causes problems with memory, thinking, and behavior. [1] It is often difficult to distinguish depression in older adults without cognitive changes versus depression in those affected with Alzheimer's dementia. Depression is one of the most frequent psychiatric complications of AD, affecting as many as 50% of patients.[3] To address this disparity, one must first understand the criteria in diagnosing depression in AD.

Current guidelines such as the National Institute of Mental Health-depression in Alzheimer's disease (NIMH-dAD) and the Cornell Scale for Depression in Dementia (CSDD) have been used to diagnose depression in AD.[3] Once the diagnosis of depression in AD has been made, consideration of effective treatment is required. Depression in AD is associated with greater morbidity and mortality, which does not only affect the patient but the families and caregivers, and society as a whole. [2,3] The estimated societal costs due to AD are between $100 billion per year, and are projected to double by 2020 and triple by 2040.[4,5] In addition, depression in AD may also be associated with increased risk of suicide.[6]

This review evaluated a Cochrane review as well as two other clinical trials to examine the efficacy of SSRI's at reducing depressive symptoms in AD. The conclusion suggested that there is weak evidence to support the use of SSRI's in the treatment of patients with AD and depression. However, this conclusion is based on a small number of studies with small sample sizes.[11] In order to decrease morbidity and mortality among patients with AD who suffer with depression, there must be further research to support the efficacy of SSRI's.

Background

Cognitive function that leads to significant impairment or change in functioning is not a normal part of aging and is not inevitable. For instance, a 78-year-old woman who spends an hour finishing a crossword puzzle that used to take her 20 minutes is considered to be in a normal spectrum of aging. However, a 75-year-old man who repeatedly loses his car keys and has missed a couple doctor's appointments he forgot to write down is considered to have mild cognitive impairment.[12]

Dementia interferes with one's activities of daily living and is associated with decline in executive functioning. For instance, one may no longer possess the capacity to responsibly manage one's own finances, which can have serious potential consequences. Dementia in older adults is also characterized as insidious in onset with a stable course and is associated with clear consciousness. Persons with dementia also have a relatively normal attention span, possess a global impairment in non-fluctuating cognition in terms of conceptual organization (with hallucinations usually absent), possess normal psychomotor activities, and have reduced vocabulary.[13]

Although there are many kinds of dementia, this paper will focus on AD, which is considered a more severe form of dementia. AD is characterized as a steady, gradual decline in its neurological processes, and while non-Alzheimer's dementia is characterized as possessing normal psychomotor activities, there is psychomotor dysfunction in AD. In the early stages of AD, memory dysfunction is usually the first symptom followed by apathy, depression, and anxiety. Psychotic symptoms such as delusions, hallucinations, agitation, wandering, and aggression are more prevalent during the middle stages of AD.[13]

According to the Alzheimer's Association, "for a person to be diagnosed with depression in AD, he or she must have either depressed mood (sad, hopeless, discouraged or tearful) or decreased pleasure in usual activities, along with two or more of the following symptoms for two weeks or longer: 1) social isolation or withdrawal, 2) disruption in appetite that is not related to another medical condition, 3) disruption in sleep, 4) agitation or slowed behavior, 5) irritability, 6) fatigue or loss of energy, 7) feelings of worthlessness or hopelessness, or inappropriate or excessive guilt, and 8) recurrent thoughts of death, suicide plans or a suicide attempt."[14]

According to the Alzheimer's Association, depression in AD does not always look like depression in people without AD. The ways in which they differ is that depression in a person with AD: 1) may be less severe, 2) may not last as long and symptoms may come and go, and 3) the person with AD may be less likely to talk about or attempt suicide.[1] However, depression in older adults not affected by AD is characterized as: 1) gradual in onset with a stable course, 2) clear consciousness, 3) difficulty in concentration, 4) global slowing in cognition, 5) decreased energy, 6) difficulty with activities, 7) latency in speech with low volume, and 8) general slowing of conceptual organization.[12] Depression in the elderly not affected by AD may also present atypically such as a lack of sadness, hyperactivity, and somatic complaints such as appetite changes, vague gastrointestinal symptoms, constipation, and sleep disturbances.[12]

It is important that we understand how depression affects patients with AD because it affects morbidity and mortality. According to Sergio Starkstein and Romina Mizrahi, "depression is one of the most frequent comorbid psychiatric disorders in Alzheimer dementia and other dementias, and is associated with poorer quality of life, greater disability in ADLs, a faster cognitive decline, a high rate of nursing home placement, relatively higher mortality and a higher frequency of depression and burden in caregivers. Depression in AD is markedly underdiagnosed and most patients with depression are either not treated or are on subclinical doses of antidepressants."[15]

The approach to treatment for depression in AD should start with an evaluation to characterize the nature and cause of the depressive symptoms.[8] Evaluation of depression in AD should consist of thorough history taking, mental status examination, laboratory studies, and rating on standardized measures for depression in dementia, such as the CSDD or the Dementia Mood Assessment Scale (DMAS).[3]

Once the diagnosis of depression in AD has been made, from mild to severe depression, one should assess the most appropriate treatment options. For those with mild depression, it has been suggested that therapy should start with non-biological interventions, such as the provision of pleasant activities.[9] Pharmacological management is often used for depression in AD patients who do not respond to non-biological interventions alone. Often times, pharmacological management is required for patients with a CSDD score greater than 12[10]; when the patient is

suicidal or violent or when the patient is not eating or drinking.[3] This review will focus on AD patients with depression who require pharmacological treatment for their symptoms. More specifically, this review will focus on the efficacy of selective serotonin reuptake inhibitors (SSRIs) at reducing depressive symptoms in comparison to AD patients not taking SSRIs.

Epidemiology

AD is the most common cause of dementia and one of the leading sources of morbidity and mortality in the aging population. AD is increasingly prevalent with advancing age and it is estimated that around 47 million people are affected by dementia. The onset of AD usually occurs at age greater than 65 years old, with a peak incidence between the ages of 75 to 84 years. Risk factors for AD include: advanced age, family history, hypertension, dyslipidemia, cerebrovascular disease, peripheral atherosclerosis, Type 2 diabetes and obesity, less-active lifestyle, brain trauma, and certain medications (e.g. benzodiazepines, anticholinergics, antihistamines, opioids).[16]

Pathophysiology

Amyloid beta peptides and the tau protein have been implicated in the pathogenesis of AD. Even though the exact pathogenesis of AD remains unclear, what is clear is that all forms of AD seem to share the overproduction and/or decreased clearance of a protein called amyloid beta peptides. Amyloid beta peptides are produced by the cleavage of mature protein translated from the amyloid precursor protein (APP) gene and cleaved by beta-secretase and gamma-secretase.[16]

AD is thought to be caused by a defect in presenilin, a transmembrane protein that forms part of the gamma-secretase complex. The defect in presenilin starts with genetic mutations in the code for making presenilin, presenilin 1 (PSEN1) or presenilin 2 (PSEN2), which causes the over-production of amyloid beta or more neurotoxic forms of amyloid beta. Even though the ultimate neurotoxin in AD is debated, experimental evidence highlights small aggregates of amyloid beta peptides called oligomers, as opposed to larger aggregates called fibrils that seem to contribute to AD.[16]

The pathogenesis of AD also involves a second protein, tau. Tau is a protein that aids in the assembly and stabilization of microtubules. In AD, tau becomes hyper-phosphorylated and collects to form paired helical filament (PHF) tau, which is a major component of neurofibrillary tangles within the cytoplasm of the neuron. Experiments have shown that the accumulation of this PHF tau is toxic to neurons. According to J.L. Guo and V.M. Lee, "the transmission of pathologic forms of tau between neurons has been proposed to account for the spread of AD in the brain, which follows a distinct progression across brain regions as AD advances."[17]

There are also other significant and potentially overlapping pathways that are thought to contribute to the pathogenesis of AD. One example is the human apolipoprotein E (APOE) gene. APOE is a pleiotropic lipoprotein involved in multiple cellular processes such as cholesterol transport, development, synaptic plasticity, and immune regulation.[18] There are three alleles of APOE, called epsilon 2 (e2), e3, and e4, and their encoded isoforms also vary.[18] It is postulated that inheritance of the APOE e4 may increase AD risk is by impairing amyloid beta clearance from cerebrum.

The pathophysiology of depression in AD has also been associated with the possible selective loss of noradrenergic cells in the locus ceruleus of the brain.[7] Studies have also shown that depression is associated with loss of dorsal raphe serotonergic nuclei in Alzheimer's disease.[7] These findings have implications for the treatment of depression, specifically, about the role of manipulation of the relevant neurotransmitter systems in treating AD- associated depression.[3]

Methods

PubMed was searched with the following terms: "depression in Alzheimer's," "review of SSRI depression Alzheimer's," "SSRI treatment in Alzheimer's," "efficacy of SSRI's in Alzheimer's." Google Scholar was also searched for the following terms: "depression in Alzheimer's," "SSRI's and Alzheimer's," "efficacy of SSRI Alzheimer's" and "SSRI's depression in Alzheimer's." EBSCO was also searched using the following terms: "SSRIs treating depression AND Alzheimer's." Scopus was also searched using the terms "depression AND Alzheimer's AND SSRI's."

Two randomized control trials and a systematic review was also referenced for the clinical review of this topic. Studies that involved treatment of temporary behavioral symptoms of

dementia, such as fluctuating agitation and aggression was excluded. Studies that included non-SSRI treatment for depression in Alzheimer's disease such a tricyclic antidepressants, anti-psychotics, and electro-convulsive therapy (ECT) was also excluded. Bias was evaluated with the Cochrane Risk of Bias Tool and the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system.

Results

This review included the evaluation of a Cochrane systematic review of randomized trials, as well as two clinical studies that were not included in the systematic review. Summary tables of study results, outcomes, and risk of bias are included in Tables 1, 2, 3 and 4.

Rosenberg et al. (2010) conducted a randomized, double-blinded treatment with sertraline or placebo in their study to assess the efficacy and tolerability of sertraline (an SSRI) for depression in AD. One hundred thirty-one participants from five U.S. medical centers with mild-moderate AD (Mini-Mental State Examination scores 10-26) and depression of AD were either given a placebo or 100 mg daily of sertraline.

Efficacy was assessed using logistic regressions and mixed effect models in an intention-to-treat analysis with imputation of missing data.[19] Outcome measures was assessed using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC), change in CSDD scores, and remission defined by both mADCS-CGIC score ≤ and CSDD score ≤ 6.[19] The results from their studied showed a mADCS ratings (odd ratio [OR=1.01], 95% confidence interval [CI]: 0.52-1.97m p= 0.98), CSDD scores (median difference at 12 weeks 1.2, 95% CI: 1.65-4.05, p=0.41), and remission to depression at 12 weeks of follow-up (OR=2.06, 95% CI: 0.84-5.04, p=0.11) did not differ between the experimental group (those who took sertraline 100 mg daily, n=67) versus the control group (placebo, n=64).[19] Furthermore, more patients in the experimental group reported more adverse outcomes (such as gastrointestinal and respiratory symptoms) from treatment than placebo. In so forth, the study by Rosenberg et al. (2010) suggested that 12 weeks of sertraline treatment for depression in AD was not associated with clinical improvement and was associated with a higher risk of adverse effects on the gastrointestinal and respiratory systems.

A comprehensive study conducted by Banerjee et al. (2016) consisted of a multi-center, randomized, double-blind, placebo-controlled trial to determine the clinical effectiveness of sertraline and mirtazapine in reducing depression over 13 weeks.[20] The design of their study consisted of 326 participants randomly assigned to either placebo (n=111), sertraline (n=107) or mirtazapine (n=108) in nine English old-age psychiatry services who met the following criteria: probable or possible AD, having depression for over four weeks, and a CSDD score of 8 or above.

The outcome from their study showed differences in CSDD at 13 weeks from an adjusted linear-mixed model: mean difference (95% CI) placebo-sertraline 1.16 (-.023 to 2.78; p=0.102); placebo-mirtazapine 0.01 (-1.37 to 1.38; p=0.991); and mirtazapine-sertraline 1.16 (-0.27 to 2.60; p=0.112).[20] It was also reported that the placebo group had fewer adverse reactions (29/111, 26%) than sertraline (46/107, 43%) or mirtazapine (44/108, 41%; p=0.017) and that each group had an equal mortality rate at 39 weeks.[20] The results suggested that the antidepressants are not clinically effective (compared with placebo) for clinically significant depression in AD and suggests that patients have less gastrointestinal side effects with placebo versus sertraline.

A 2009 Cochrane systematic review aimed to determine whether antidepressants are clinically effective and acceptable for the treatment of patients with depression and dementia.[11] The authors searched the Cochrane Dementia and Cognitive Impairment Group (CDCIG) Specialized Register for clinical trials, contacted the medical information departments of pharmaceutical companies for ongoing clinical trials, and contacted the authors of the clinical trials themselves for additional information. The selection criteria the authors used consisted of non-confounded, double-blind, randomized trials of longer than 4 weeks, comparing any antidepressant drug with placebo, for patients diagnosed as having dementia and depression. Diagnostic and Statistical Manual of Mental Disorders (DSM), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and International Classification of Disease, Tenth Edition (ICD-10) criteria for dementia and depression were met for participants and consisted of patients of any age and sex. Patients suffering from emotional disorders or behavioral problems, but falling short of depression (as diagnosed by the recognized criteria) were excluded.[11] Any antidepressant medication listed in the British National formulary number 49, 2005, section 4.3 compared with

placebo were included in their review.[11] Those trials which studied euphoriants (e.g. amphetamines), adjuvants (e.g. lithium), combination treatments (e.g. 'Motipres') and studies of other drug classes not generally regarded as antidepressants in the first instance (e.g. antipsychotics) were excluded.[11]

The search methods included trials from CENTRAL, MEDLINE, EMBASE, PsychINFO, CINAHL, SIGLE, ISTP, INSIDE, Aslib Index to Theses, Dissertation Abstract, ADEAR, and the National Research Register. The search also included current control trials from the Alzheimer Society, GlaxoSmithKline, HongKong Health Services Research Fund, Medical Research Council (MRC), NHS R&D Health Technology Assessment Programme, Schering Health Care Ltd., South Australian Network for Research on Ageing, U.S. Department of Veterans Affairs Cooperative Studies, and the National Institutes of Health. The authors also searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group with mention of a detailed list of search terms.

Standard chi-square statistic was used to assess heterogeneity of the treatment effect between the trials. If a test of heterogeneity was negative, then a fixed effects model was used.[11] If there was heterogeneity of the treatment effect in a study, then only the homogenous results or a random effects models was used. The authors also calculated the odds ratio for each trial and then a pooled odds ratio across appropriate groups of trials using Mantel-Haenszel methods. The weighted mean difference between treatment and control was used for continuous variables.

Seven studies met inclusion criteria with a total of 1140 participants. The mean length of the studies was 6-12 weeks and dementia was categorized in a variety of ways: "primary degenerative dementia, probable Alzheimer's disease, dementia, Alzheimer's disease, probable Alzheimer's disease, and primary degenerative dementia of the Alzheimer's type, with all participants meeting DSM criteria for dementia or NINCDS-ADRDA criteria for probable Alzheimer's disease."[11]

Primary outcomes of interest were effect on depression (measured by rating scales), effect on cognitive function (measured by psychometric tests), global impression, acceptability of treatment (as measured by withdrawal from trial), and safety (as measured by the incidence of adverse effects and withdrawal from the trial).[21] Risk of bias was addressed in which the

authors used only double-blinded studies. However, there was no further investigation on the degree to which the trials were double-blinded and the nature of the placebos was not stated in three of the studies.[11]

The review included two studies that investigated SSRI's in the treatment of depression in Alzheimer's (Lyketsos 2003 and Petracca 2001). The Lyketsos 2003 study produced two significant differences in favor of treatment with SSRI's in the CSDD at 12 weeks (95% CI -11.50 – 1.90) and in the psychiatrist's global rating (Peto odds ratio (OR) (95% Fixed) 7.33 (2.20, 24.46)).[11] However, the meta-analysis showed a significant difference in favor of placebo (Peto OR (95% Fixed) 1.42 (1.07, 1.89), with patients experiencing at least one adverse event, such as one nervous system adverse event, gastrointestinal symptoms, and dry mouth with SSRI's.

Table 1. Summary of findings of treatment for depression with SSRI's vs. Placebo

mADCS-CGIC[a] Rating	Sertraline, n = 67[b]	Placebo, n = 64
7 "much worse"	1 (1.5)[c]	0 (0)
6 "worse"	5 (7.5)	2 (3.1)
5 "a bit worse"	6 (9.0)	9 (14.1)
4 "no change"	10 (14.9)	11 (17.2)
3 "a bit better"	18 (26.9)	18 (28.1)
2 "better"	18 (26.9)	21 (32.8)
1 "much better"	9 (13.4)	3 (4.7)

Notes: Data are presented as n (%).

[a]Modified ADCS-CGIC was assessed at Week 12. ADCS-CGIC, a clinician-rated global impression of change from baseline through Week 12, was modified, so that the clinician was rating global impression of mood change only.

[b]These numbers include imputed values from the first imputation cycle. The analysis combined the results across five imputation cycles.

[c]Percentages may not add to 100% due to rounding.

(Rosenberg et al., 2010)

Table 2. Proportion of participants with depression

	Visit					
	Baseline		Week 13		Week 39	
Treatment	No depression	Depression	No depression	Depression	No depression	Depression
Placebo		111	47 (49%)	48	40 (49%)	42
Sertraline		107	38 (49%)	40	33 (47%)	37
Mirtazapine		108	42 (49%)	43	42 (55%)	34
Total		326	127	131	115	111

Number (%) of cases of depression.

(Banerjee et al., 2016)

Table 3. Odds ratio, the Neuropsychiatric Inventory (NPI) and derived factor scores

	Week 13	Week 39
NPI factor: OR (SE); 95% CI; (*p*-value)	Sertraline vs placebo	Sertraline vs placebo
Total score	1.098 (0.12); 0.884 to 1.363; (0.397)	1.150 (0.15); 0.884 to 1.495; (0.298)
Factor 1	1.104 (0.19); 0.782 to 1.558; (0.573)	1.101 (0.233); 0.728 to 1.666; (0.649)
Factor 2	1.203 (0.22); 0.840 to 1.723; (0.313)	0.996 (0.18); 0.697 to 1.425; (0.984)
Factor 3	1.395 (0.26); 0.964 to 2.018; (0.078)	1.663 (0.42); 1.020 to 2.713; (0.042)
Factor 4	1.064 (0.18); 0.762 to 1.486; (0.715)	1.141 (0.21); 0.786 to 1.656; (0.488)

a fully adjusted modelling.

(Banerjee et al., 2016)

Table 3. Adverse reactions of SSRI's by Week 39 of treatment

Classification	Treatment group			Total events
	Placebo	Sertraline	Mirtazapine	
Psychological	10 (22)	9 (18)	24 (44)	53 (84)
Neurological	8 (9)	16 (25)	18 (21)	42 (55)
Gastrointestinal	7 (7)	20 (24)	11 (13)	38 (44)
Other	2 (2)	5 (5)	3 (3)	10 (10)
Genitourinary	4 (4)	3 (3)	2 (3)	9 (10)
Musculoskeletal	2 (3)	3 (3)	3 (3)	8 (9)
Dermatological	3 (4)	3 (3)	2 (2)	8 (9)
Respiratory	2 (2)	1 (1)	2 (2)	5 (5)
Cardiovascular	1 (1)	0 (0)	2 (4)	3 (5)
Infection	1 (1)	1 (1)	1 (1)	3 (3)
ENT	2 (2)	1 (1)	0 (0)	3 (3)
Haematological	1 (1)	1 (1)	0 (0)	2 (2)
Endocrine	0 (0)	1 (1)	0 (0)	1 (1)
Total[a]	29 (58)	46 (86)	44 (96)	119 (240)

ENT, ear, nose and throat.
a Data are number of participants (number of events).

(Banerjee et al., 2016)

Table 4. Cochrane Risk of Bias Evaluation

	Rosenberg et al., 2010	Banerjee et al., 2016
Random sequence generation	+	+
Allocation concealment	+	+
Blinding of participants and personnel	+	+
Blinding of outcomes assessment	+	+
Incomplete outcome data	+	+
Selective reporting	+	-
Other bias	+	+

Discussion

The study conducted by Rosenberg et al. (2010) showed that depression severity improved by nearly 50% (by CSDD scoring) with sertraline. However, when compared with the placebo group (which also showed an improvement of depression severity), there was no significant difference. The authors suggest that psychosocial intervention may have impacted study outcomes given the high rate of placebo response, which dilutes observed drug effect.[19] Another significant finding was that the sertraline group was associated with an increased

incidence of adverse reactions, particularly those involving the respiratory system due to eosinophilic pneumonitis. Ultimately, the authors concluded that sertraline did not demonstrate efficacy for the treatment of depression in patients with AD and that SSRI's may be of limited value for treating depression in patients with AD.[19]

The study conducted by Banerjee et al. (2016) addressed barriers to their comprehensive study, particularly with regards to generalizability. The researchers stated that "dropout introduced bias if those dropping out had a different response to the trial interventions or placebo compared with those completing the trial."[20] They also mentioned that their study may not generalize to those populations who are at high risk of suicide because that group cannot risk randomization. Furthermore, the groups enlisted in their study are part of a specialist service for old-age psychiatry and do not include those with Alzheimer's dementia who are in primary care facilities. The authors concluded that antidepressants appear to be no more effect than placebo.

The Cochrane Review mentions the complexity of diagnosing depression in patients with AD. For instance, the DSM criteria for depression includes anhedonia and poor concentration, both symptoms of dementia.[11] Sample size was also mentioned as a limiting factor for the clinical trials involving SSRI's for the treatment of depression in patients with AD. For instance, "there was a significant difference in favor of treatment compared with placebo in the CSDD at 12 weeks and in the psychiatrists' global rating…[however], both of these results originate from a single study (Lyketsos 2003) with a small sample size (n = 44)."[11] Thus, making the generalizability of SSRI's in the treatment for depression in patients with AD questionable.

Conclusion

Even though there was a lack of clinically significant outcomes in the trials between the use of SSRI's vs. placebo in treating depression in Alzheimer's disease, that does not mean that SSRI's are ineffective. SSRI's have been the first-line treatment for many patients with depression due to their favorable risk-benefit ratio.[23] There were a few key issues that were addressed among the trials. Firstly, it is challenging to diagnose depression among patients with AD because symptoms such as difficulty concentrating and the inability to feel pleasure are also characteristic of both dementia and depression, making delineation difficult. There have been some clinical

trials in which cognitive functioning was a measure as to the efficacy of SSRI's, however, this is non-specific to depressive symptoms.

In order to effectively begin treating depression in AD, we must use a standardized grading scale to diagnose depression that is specific in AD. CSDD and the NIMH-dAD aim to be more specific guidelines to aid providers in diagnosing depression in Alzheimer's. Such measures include categories in mood-related signs (e.g. anxiety, sadness, lack of reactivity to pleasant events, irritability), behavioral disturbance (e.g. agitation, retardation, multiple physical complaints, loss of interest), physical signs (e.g. appetite loss, weight loss, lack of energy), cyclic functions (e.g. diurnal variation of mood, difficulty falling asleep, multiple awakenings during sleep, early morning awakening), and ideation disturbance (e.g. suicide, poor self-esteem, pessimism, mood-congruent delusions).[22]

Another area of improvement for research in treating depression in AD is that there must be clinical trials with larger sample sizes to improve the generalizability of the findings. Small sample sizes are problematic because they do not adequately represent the population of AD. It was also mentioned that most of the participants in the study were part of a specialist service for old-age psychiatry and did not include those with Alzheimer's dementia who are in other facilities or in the community. Perhaps screening for depression in AD in the primary care setting can be included in future studies to address this issue.

Studies have shown that there is higher morbidity and mortality for people with AD who have comorbid depression. Further research on this topic becomes increasingly important because of the aging population in the world, as well as the growing number of people who are being diagnosed with AD annually.

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