

Depression in Dementia and Therapeutic Approaches: A Review

Demansta Görülen Depresyon ve Tedavi Yaklaşımları: Bir Gözden Geçirme

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As the elderly population is growing, mental diseases, particularly dementia and depression are assumed to be the primary diseases that health professionals are going to deal with. Depressive expressions of variable intensity may be observed in approximately 50% of dementia patients. This review aims to determine whether antidepressants are clinically effective and satisfactory for the treatment of patients diagnosed as having depression and also diagnosed as having dementia. Etiology, diagnosis, natural progression, impact on caregivers or efficacy of any treatment for depression in dementia, and also its diversity and prognosis in other types of dementia is not fully understood. As a conclusion; various antidepressant drugs have been used for treatment of dementia. There is rare data on how to use antidepressants in dementia patients with depression. However, keeping their drug interactions in mind, we believe that use of SSRIs together with non-pharmacologic measures will be beneficial to prevent capacity loss in depressive dementia patients. However further investigation into the prevalence, diagnosis, etiology and treatment of depression among dementia patients at end of life is necessary.

Key words: Dementia; depression; treatment.

Yaşlı nüfusun giderek artmasıyla birlikte demans ve depresyon başta olmak üzere mental hastalıklar, sağlık profesyonellerinin ilgilendiği primer hastalıklar olarak kabul edilmektedir. Depresif durumlar demanslı hastalarda %50'ye varan değişik yoğunlukta gözlenebilmektedir. Bu gözden geçirme çalışmasının amacı, demans komorbid depresyonu bulunan hastalarda kullanılan antidepressanların klinik olarak tatmin edici etkisinin olup olmadığını araştırmaktır. Demansın etyolojisi, tanısı, doğal süreci, bakıcılar üzerine etkisi veya demansta depresyonun tedavisi ve diğer demans tiplerinin farklılığı ve prognozu tam olarak anlaşılamamıştır. Sonuç olarak çeşitli antidepressan ilaçlar demanslı hastalarda kullanılmaktadır. Depresyonlu demans hastalarında bu ilaçların nasıl kullanılacağı üzerine sınırlı sayıda veri vardır. Bununla birlikte ilaç etkileşimlerini de hesaba katarak spesifik serotonin gerilim inhibitörleri'nin non farmakolojik yaklaşımlarla birlikte tercih edilmesinin depresif demans hastalarının işlevselliğine faydalı olabileceği kanaati oluşmuştur. Ancak yaşamın son dönemindeki demanslı hastalardaki depresyonun yaygınlığı, tanısı, etyolojisi ve tedavisi üzerine daha fazla araştırma yapılması gerekmektedir.

Anahtar sözcükler: Demans; depresyon; tedavi.

As the elderly population is growing, mental diseases, particularly dementia and depression are assumed to be the primary diseases that health professionals are going to deal with.⁽¹⁾ Community studies show mild dementia in 2.6-20% and

severe dementia in 1.3-6.2% of the individuals over 65.⁽²⁾ Incidence of major depression is reported between 1 and 10%.⁽³⁾ These figures are increased among the residents of social institutions, individuals with medical diseases or demen-

tia. Incidence of depression may be as high as 13-50% among the residents of social institutions.⁽⁴⁻⁶⁾ In our country major depression is observed in 6-35% of the general population over 65, but its frequency increases up to 10.2-48.1% among the residents of social institutions.⁽⁷⁻¹¹⁾

Depressive expressions of variable intensity may be observed in approximately 50% of dementia patients.⁽¹²⁾ In one study on dementia patients, this rate was reported to be as high as 86%.⁽⁴⁻⁶⁾ These figures range from 17 to 31% in Alzheimer's Disease (AD).⁽¹²⁾ Depression is observed in 25% of the patients with cerebrovascular diseases. In addition to AD or cerebrovascular syndrome, depression may be observed in 50% of the patients with Parkinson disease. Inconsistency between the results of these studies may be explained by evaluation of patients in different stages of their disease, by use of different diagnostic criteria for either AD or depression and various clinical methods to evaluate mood alterations.⁽¹²⁾

The neurobiological basis of depressive symptoms in AD is not fully understood, but functional defects of noradrenergic and serotonergic systems are considered in the etiology. It is well known that locus ceruleus and raphe nucleus is affected in AD. Limbic structures and dorsolateral frontal regions involved in the pathophysiology of depression are also affected in AD. Presence of positive family history for depressive disorders in the AD patients that experienced depression suggests that hereditary factors may play role in determination of which AD patient will develop depressive symptoms by time.⁽¹³⁾ Additionally, reduction of cortical cholinergic neurons constitutes one of the main reasons that are recognized to cause cognitive deficits in AD and dementia with Lewy bodies. Most of these individuals show depressive and extrapyramidal symptoms due to degeneration of serotonergic, noradrenergic and dopaminergic neurons.⁽¹⁴⁾

This review aims to determine whether antidepressants are clinically effective and satisfactory for the treatment of patients diagnosed as having depression and also diagnosed as having dementia.

Two psychiatrists evaluated available evidence from a structured literature using Medline (PubMed) from 1990 to 2007. Keywords was dementia, depression and treatment in the searching.

DIAGNOSIS

Clinical picture of "complicated dementia" where dementia is associated with mixed agitation and depression is described as a subgroup. These patients deteriorate with rapid decrease in functionality and loss of cognitive function accompanied by social isolation. Expanding medical comorbidities; and need for major psychiatric treatment increase the costs. It is essential to describe this subgroup for depiction of treatment guide and drug combinations in complicated dementia.⁽¹⁵⁾ High response rates to medical or electroconvulsive therapy (ECT)⁽¹⁴⁾ underlines the importance of diagnosis of these patients. But diagnosis is not always straightforward in these patients. Depression may exhibit different symptoms in dementia patients. For example, persisting pain in dementia patients living in the institutions has been found to be associated with depression.⁽¹⁶⁾

Higher rates of depression are reported among dementia patients attending psychiatry centers and patients with mild to moderate dementia. Depressive symptoms can be better recognized by using expressions of the patients' relatives rather than the subjective evaluation of the interviewer.⁽¹²⁾ As dementia progresses, development of symptoms such as difficulties of language and communication, apathy, and agitation obscure the diagnosis.⁽¹⁷⁾ In this case, measurement tools are required to determine depression in dementia patients. Scales that uses self-report such as Geriatric Depression Scale that is widely used in the clinical practice has limited efficacy due to recalling problems in dementia patients.⁽¹⁸⁾ Cornell Depression Scale in Dementia developed by Alexopoulos et al.⁽¹⁹⁾ better recognizes depressive symptoms of dementia patients by using information both from the patient and the caregiver. Symptoms related to mood, behavioral changes, physical findings, cyclic functions and intellectual changes are assessed in the scale.⁽²⁰⁾

DIFFERENTIAL DIAGNOSIS

Depression is the primary disease that must be considered in differential diagnosis. Depressive manifestations together with symptoms and signs of dementia (pseudo dementia) may cause difficulties in diagnosis. Vegetative characteristics of both diseases are similar, but symptoms such as loss of interest, lack of energy, difficulty in concentration, agitation and retardation observed in

Table 1. Discrimination of Dementia and Depression.

	Primary Depression	Primary Dementia
History of depressive episode	Usually positive	Usually negative
Family history	History of depression (+)	History of dementia (+)
Onset	Acute	Insidious
Sundowner syndrome	Absent	Present
Complain of cognitive disorder	Present	Absent
Response	I don't know	Close to truth
Memory	Short-long term memory equally affected	Short-term memory more affected
Praxia and recognition	Normal	Deficient

early stage AD disease may lead to misdiagnosis of depression. Sadness or sorrow mood and mental status was found to be more helpful to discriminate depressive dementia patients from depressive patients. Discrimination of dementia from depression is summarized in Table 1.⁽²¹⁾ There is history of depressive episode, complain of cognitive disorder and loss of short-long term memory in depression. The other discriminations are in Table 1.

Apathy also seen in frontal lobe syndrome may be diagnosed as delayed depression.⁽¹²⁾ Apathy or psychomotor retardation may be caused by various medical situations. Carcinoma, cardiac disease, cerebrovascular insufficiency, endocrinopathy (particularly thyroid disease), chronic infection and advanced anemia must be investigated especially in patients with resistant depression.⁽²²⁾ Adverse effects of some drugs may also mimic depression.

TREATMENT ACCORDING TO EVIDENCE-BASED MEDICINE

Although frequently coexists, depression in dementia patients is not recognized, and certainly not treated.⁽²³⁾ Treatment of these patients is of vital importance. If untreated, their morbidity and mortality rates are increased.⁽¹⁷⁾ Their impaired cognitions further deteriorate. Social isolation develops and their quality of life diminishes. Rate of admission to social institutions or hospitals is increased. Workload on caregivers is amplified thereby increasing the incidence of depression among the caregivers. These patients are usually mistreated because they cannot be recognized. Anxiolytics and hypnotics rather than antidepressants are used in these patients.⁽²⁴⁾

Treatment includes assessment of exogenous factors and consideration of some other points. For example correction of environmental conditions, treatment of underlying diseases if present, review of drugs used for other systemic disease, cessation of unnecessary medication (anticholinergic, tricyclic antidepressives, benzodiazepines etc.) may be required. It is not possible for dementia patients to achieve their treatment by themselves. In USA 28% of the elderly are hospitalized for drug-related problems.⁽²⁵⁾ Worst association between drug and injury is established between psychotropic drugs and hip fractures.⁽²⁶⁾ Thus instruction of caregivers about drugs and the treatment is crucial.

Mild depressive symptoms do not require psychotropic; they should be used in conjunction with non-pharmacologic approaches in presence of moderate to severe symptoms. And there is no obligation that all patients with symptoms receive drug medication. But if medication is going to be used, basic principle should be “start with low dose, increase steadily, but treat with effective doses”.⁽¹⁷⁾

Various antidepressant drugs have been used for treatment of AD. The limits for using antidepressant treatment constitute a special consideration for these patients. However there is scarce data on how to use antidepressants in dementia patients with depression.⁽²⁴⁾

Studies on antidepressants have yielded conflicting results. Some studies reported no superiority of antidepressants over placebo. For example, a meta-analysis of 6 studies, three of which were double-blind placebo-controlled studies, showed “poor evidence” for efficacy of antidepressants in

dementia.⁽²⁷⁾ But study was not large enough. Imipramine was found to be ineffective in these patients.⁽²⁸⁾ Double-blind placebo controlled study of fluoxetine has also showed discouraging results.⁽²⁹⁾ Two studies on sertraline that have been implemented on different time periods also yielded negative outcomes.^(30,31) A serotonin noradrenaline reuptake inhibitor (SNRI) drug venlafaxine is accepted as drug of choice together with SSRIs for geriatric depression,⁽³²⁾ but a recent double-blind, randomized, placebo controlled study lasted for 6 weeks showed no superiority of venlafaxine over placebo in dementia patients with depression. But relatively short study period, inhomogeneous types of dementia, small number of cases and low dose of drug are the shortcomings of this study.⁽³³⁾

Despite these negative results, majority of the depressive dementia patients respond to antidepressant treatment. Deprenyl used for AD patients (irrespective to their mood); has led to improvement in anxiety/depression, activation, anergy, hostility and impaired cognition subscales of Short Psychiatric Evaluation Schedule.⁽¹³⁾ A double-blind placebo-controlled study on clomipramine 25 to 100 mg/day in 24 AD patients showed statistically significant improvement in these patients.⁽³⁴⁾ Especially studies showing efficacy of SSRIs are gaining importance. Citalopram has been shown to be effective on agitation, anxiety and depressive symptoms in 10-20 mg doses.⁽³⁵⁾ Another study has proved benefit of citalopram on depressive dementia.⁽³⁾ There are studies that proved the efficacy of sertraline which is another SSRI. In a double-blind randomized controlled study, 95 mg/day sertraline treatment for 12 weeks showed significant improvement over placebo on 44 patients with AD and Major Depression.⁽³⁶⁾ Another study on sertraline showed that this psychotropic agent corrected refusal of nutrition and affective symptoms.⁽³⁷⁾ Antidementia drugs have been shown to be effective especially in neuropsychiatric symptoms of apathic AD patients,⁽³⁸⁾ and their use is recommended in dementia patients with major apathy despite lack of controlled studies. An international, double blind controlled study on moclobemide demonstrated positive effects in 400 mg/day dose.⁽¹⁾ More than half of depressive patients with dementia living in the institutions have used various antidepressants and obtained some benefit.⁽¹⁵⁾ There are also se-

veral comparative studies. In a study that compared fluoxetine and amitriptyline similar efficacy was observed but fluoxetine was better tolerated.⁽³⁹⁾ Another study that compared paroxetine and imipramine showed similar efficacy⁽⁴⁰⁾ but paroxetine was better tolerated.

Recently there are several studies on a multipurpose drug ladostigil. This drug has been shown to selectively inhibit butyrylcholinesterase, acetylcholinesterase, monoaminoxidase (MAO)-A, MAO-B enzymes and improve forgetfulness and produce anxiolytic, antidepressive effect on rats. This drug is supposed to be beneficial for depression associated with dementia in the future.⁽⁴¹⁾

ECT may be used in patients with psychotic depression associated with dementia although there is risk of confusion after ECT.^(12,42,43) But it has to be compared with medical treatment and its long term results, long-term efficacy and possible long-term side effects on cognitive function need to be determined.

PSYCHOTROPIC TREATMENT IN SPECIFIC MEDICAL SITUATIONS

Psychopharmacology is the most active branch for research and development in clinical medicine. Discovery of a new psychoactive drug each day further puts emphasis on this field. Limited development has been achieved in pharmacology between 1960 and 1980, but there is an outburst of information in the recent years and everyday a new drug is discovered and introduced for treatment. Preference of a drug for any psychiatric disorder not only involves prescription of any drug, but the drug that effects physical function, mental status, family relations, and professional life and if present other physical disorders; or drug that show interaction with the drugs for these disorders is selected.⁽⁴⁴⁾ Table 2 describes some specific medical situations and risk of the antidepressant and anxiolytic-hypnotic drugs that may be used.⁽⁴⁵⁾ It is essential to prefer the antidepressant with least side effect according to specific condition of each patient. Foreexample if the patient has epilepsy venlafaxine should not be preferred. The other information about this subject in Table 2.

DRUG INTERACTIONS

Drug-drug interactions continue to be misunderstood by most clinicians. Drug interactions

Table 2. Risk of Psychotropic Agents According to Medical Situations.

ELDERLY PATIENTS			
	Low Risk	Medium Risk	High Risk
<u>Antidepressants</u>	Mirtazapine Moclobemide SSRIs Venlafaxine	MAO-Inh Mianserin Reboxetine Trazodone	Tricyclics
<u>Anxiolytics, Hypnotics</u>	Alprazolam Buspirone Lorazepam	Propranolol	Long acting benzodiazepines
CARDIOVASCULAR DISEASES			
<u>Antidepressants</u>	Mirtazapine SSRIs Trazodone Mianserine	MAO-Inh Moclobemide Reboxetine	Tricyclics Venlafaxine
<u>Anxiolytics, Hypnotics</u>	Benzodiazepines Buspirone	Beta-blockers Chloral Hydrate	
DIABETES MELLITUS			
<u>Antidepressants</u>	SSRIs Venlafaxine Trazodone Moclobemide Reboxetine	Fluoxetine Mirtazapine Mianserine Tricyclics	MAO-Inhibitors
<u>Anxiolytics, Hypnotics</u>	Benzodiazepines Buspirone	Beta-blockers	
EPILEPSY			
<u>Antidepressants</u>	SSRIs Moclobemide Reboxetine MAOI-Inh	Venlafaxine Trazodone Mirtazapine Mianserine Tricyclics Buspirone	Maprotiline
<u>Anxiolytics, Hypnotics</u>	Benzodiazepines Beta-blockers		
GLAUCOMA			
<u>Antidepressants</u>	Venlafaxine Moclobemide MAOIs Trazodone Benzodiazepines	SSRIs Mirtazapine	Tricyclics
<u>Anxiolytics, Hypnotics</u>			
LIVER DISEASES			
<u>Antidepressants</u>	Mianserine Paroxetine	Mirtazapine Moclobemide Reboxetine SSRIs Trazodone Tricyclics Venlafaxine	MAOI-Inhibitors
<u>Anxiolytics, Hypnotics</u>	Lorazepam	Buspirone Clomethiazole Propranolol LD	Benzodiazepines Propranolol HD
RENAL FAILURE			
<u>Antidepressants</u>	Mianserine Moclobemide Tricyclics Trazodone	MAO-Inh Mirtazapine Reboxetine SSRIs	Fluoxetin Venlafaxine
<u>Anxiolytics, Hypnotics</u>	Some Benzodiazepines	Benzodiazepines Beta-blockers	Buspirone

Table 3. Enzymes of Cytochrome P-450 System Inhibited by SSRIs.

Drug	2D6	2C19	1A2	3A4	2E1	2C9
Fluoxetine	+	+		+		+
Citalopram				+		
Fluvoxamine	+	+	+	+		+
Paroxetine	+	+		+		+
Sertraline	+			+		+

*: Represents higher inhibition.

may be further complicated by genetic differences in metabolic capacity. Patients who routinely require long-term treatment for depression have an increased likelihood of experiencing a drug-drug interaction since they will take over-the-counter and prescription medications for intercurrent and/or co-morbid illness. Antidepressants can be the object of drug interactions when their metabolic pathways are affected by other substances, or they can precipitate interactions by inhibiting enzyme pathways. Clinicians can improve the short- and long-term outcomes of patients with a depressive disorder by considering the possibility of drug-drug interactions both before prescribing a specific antidepressant and while monitoring for response, adverse effects and patient compliance.⁽⁴⁶⁾

Some points to consider for drug interactions:

1. A psychotropic drug with the least side effects should be preferred.
2. Metabolism of other drugs that will be used concomitantly should be known.
3. Least effective dose should be used.
4. Drugs that have proven to be effective in the past should be preferred.
5. Treatment should be as simple as possible.

6. Polypharmacy should be avoided.

7. If drugs will be changed, one drug must be changed at a time.

Usually SSRIs are preferred for dementia patients in depression.⁽⁴⁷⁾ Although one SSRI may be more efficacious or better tolerated by elderly patients than another, existing data do not support such claims. However, other distinguishing features may influence the choice of agent. For example, fluoxetine, fluvoxamine and paroxetine are more likely to be involved in significant drug-drug interactions than are citalopram or sertraline (Table 3). In contrast to the other SSRIs, fluoxetine has a half-life well in excess of 1 day, which can be an advantage when weaning the patient off therapy in that it may reduce the incidence of discontinuation symptoms, but a significant disadvantage if the patient cannot tolerate the drug or experiences an adverse drug-drug interaction.⁽⁴⁸⁾ SSRIs may inhibit some CYP 450 enzymes and demonstrate high binding for plasma proteins. Table 3 presents the list of enzymes in cytochrome P-450 system inhibited by SSRIs.⁽⁴⁷⁾ SSRIs may increase the blood levels of some drugs metabolized by these enzymes.

As a conclusion; etiology, diagnosis, natural progression, impact on caregivers or efficacy of any treatment for depression in dementia, and also its diversity and prognosis in other types of dementia is not fully understood. Various antidepressant drugs have been used for treatment of dementia. There is rare data on how to use antidepressants in dementia patients with depression. However, keeping their drug interactions in mind, we believe that use of SSRIs together with non-pharmacologic measures will be beneficial to prevent capacity loss in depressive dementia patients. However further investigation into the prevalence, diagnosis, etiology and treatment of depression among dementia patients at end of life is necessary.

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