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# Depressive Syndromes in Dementia

Lilian Thorpe, Bernard Groulx

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**ABSTRACT: Background:** Depressive syndromes in dementia are common, treatment is challenging and controlled intervention studies are small in number. The goal of this paper is to review known information about the etiology, epidemiology and treatment of these syndromes, as summarized at the recent Canadian Consensus Conference on Dementia. **Methods:** A number of Medline searches were performed (most recently updated in October 2000) using the subject categories dementia and depression, or apathy or emotional lability and other relevant articles were also reviewed. The background article was edited and amended at the Consensus Conference on Dementia. Final recommendations appearing in the summary article by Patterson et al were accepted by the group consensus process. Clinical discussion and informational updates were added for the current text by the authors. **Results:** Depressive syndromes, ranging in severity from isolated symptoms to full depressive disorders, increase in dementia. While clear-cut depressive disorder is increased in this population, sub-syndromal disorders are even more common and cause considerable distress. Antidepressant treatment may improve the quality of life in depressed, demented people, although it is less successful than in those without cognitive impairment and carries more risk of iatrogenic effects. **Conclusions:** Physicians should be alert to the presence of depressive syndromes in dementia. Depressive illness should be treated and, when necessary, referral should be made to an appropriate specialist. Treatment must minimize iatrogenic effects. Although there is some support for treatment of syndromes that do not meet criteria for depressive disorder or dysthymia, the first line of intervention in these situations should involve nonpharmacological approaches.

**RÉSUMÉ: Syndromes dépressifs dans la démence. Introduction:** Les syndromes dépressifs sont fréquents dans la démence, leur traitement est un défi et il existe peu d'études d'intervention contrôlées. Le but de cet article était de revoir les connaissances sur l'étiologie, l'épidémiologie et le traitement de ces syndromes, conformément au résumé fait à la Conférence canadienne de consensus sur la démence. **Méthodes:** Des recherches dans Medline ont été effectuées (avec mise à jour en octobre 2000) utilisant la démence et la dépression comme catégorie de sujet ou l'apathie ou la labilité émotionnelle, et d'autres articles pertinents ont également été révisés. L'article de référence a été édité et amendé à la Conférence de consensus sur la démence. Les recommandations finales apparaissant dans l'article de Patterson et al sous forme de résumé ont été acceptées par consensus au sein du groupe. Les discussions cliniques et les mises à jour de l'information ont été ajoutées par les auteurs pour cette publication. **Résultats:** Les syndromes dépressifs, dont la sévérité va de symptômes isolés au syndrome dépressif, sont plus fréquents dans la démence. Bien que la maladie dépressive franche soit augmentée dans cette population, les formes mitigées sont encore plus fréquentes et causent beaucoup de détresse. Le traitement antidépresseur peut améliorer la qualité de vie chez les sujets déments qui sont déprimés, même si ce traitement est moins efficace que chez ceux qui n'ont pas de dysfonction cognitive et les risques d'effets iatrogéniques sont plus grands. **Conclusions:** Les médecins devraient être vigilants pour détecter la présence de syndromes dépressifs chez les patients déments. La maladie dépressive devrait être traitée et les patients devraient être dirigés en spécialité au besoin. Le traitement doit minimiser les effets iatrogéniques. Bien qu'il y ait des données supportant le traitement de syndromes qui ne rencontrent pas les critères de la dépression ou de la dysthymie, l'intervention de première ligne dans ces situations devrait impliquer des approches non pharmacologiques.

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This paper was initially developed as a background paper for the Canadian Consensus Conference on Dementia, organized by the Consortium of Canadian Centres for Clinical Cognitive Research (C5R), which was held in Montreal, February 27-28, 1998. Overall goals and objectives, as well as procedures for consensus development, were based on the Canadian Medical Association guidelines for clinical practice guidelines,<sup>1</sup> as described in the summary article by Patterson et al.<sup>2</sup>

In this paper we present general information about the association between depression and dementia, then summarize various clinical presentations in dementia that have prominent depressive features, review diagnostic difficulties and lastly summarize treatment of depressive disorder in dementia in more detail, culminating in the main consensus conference recommendations.

An initial Medline search was performed prior to the

consensus meeting and updated at various points in the publication preparation phase, most recently in October 2000, using the subject categories dementia, with depression, or apathy, or emotional lability. Relevant articles cited in various review articles were also reviewed. The background article was precirculated to delegates to the Consensus Conference on Dementia and treatment recommendations edited and amended at the conference. Final recommendations appearing in the

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From the University of Saskatchewan, Saskatoon, SK (LT), and McGill University; Centre for Studies in Aging, Montreal QC (BG), Canada.  
Reprint requests to: L Thorpe, Department of Psychiatry, University of Saskatchewan, Saskatoon City Hospital, 701 Queen Street, Saskatoon SK Canada S7K 0M7

summary article by Patterson et al<sup>2</sup> were accepted by the group consensus process.

Of the recommendations relating to depressive disorders in dementia, the most important ones (full text later in the document) were:

- As depressive syndromes are common in patients with dementia, physicians should consider diagnosing depression when presented with the subacute (i.e. weeks, rather than months to years) development of symptoms characteristic of depression such as behavioural symptoms, weight and sleep changes, sadness, crying, suicidal statements or excessive guilt.
- Depressive illness in dementia should be treated and, when refractory, referral should be made to an appropriate specialist.

Clinical discussion, general clinical updates and tables were added for the current text by the authors after receiving reviewers' comments. In this final document, priority was given to double-blind, placebo-controlled (DBPC) studies in the clinical recommendations.

## INTRODUCTION

In the 1989 Canadian Consensus Conference on the Assessment of Dementia,<sup>3</sup> held in Montreal, the section relating to depression was entitled "Distinguishing depression from dementia". The change of title in this consensus paper to "Depressive syndromes in dementia" reflects the improved understanding of depressive symptoms in dementia as being an integral part of the illness rather than a completely separate entity. Aside from the obvious adverse effects on quality of life, some behaviours such as aggression, which are related significantly to caregiver burden and early institutionalization, may also be closely associated with depression superimposed on dementia, so the recognition of these syndromes is very important.<sup>4</sup>

As well as recognizing depressive syndromes within dementia, it is important to recognize depression that presents (and may masquerade) as cognitive impairment, so that appropriate therapy can be instituted. Small noted in 1991<sup>5</sup> that depression detection rates in the elderly are low across various studies of primary care physicians. The accuracy of diagnosis may depend on the professional discipline involved: Verhey et al<sup>6</sup> studied the referral diagnoses to their multidisciplinary dementia clinic and noted that psychiatrists tended to under-diagnose dementia, neurologists tend to under-diagnose depression and general practitioners' diagnoses agreed most closely with the team diagnosis. Among raters of depression in demented people, family caregivers have reported the highest frequency of depressive symptoms in some studies.<sup>7</sup>

Emery and Oxman<sup>8</sup> suggest that many of the patients whose depression initially presents as dementia have significant associated organic abnormalities and will eventually go on to develop ongoing cognitive impairment. However, the appropriate treatment of the depression will usually improve the quality of life of these patients for quite some time and frequently also improve their cognitive, affective<sup>6</sup> and general functioning.<sup>7</sup>

Since treatment with antidepressants of all types can cause significant morbidity (see below), it is important that clinicians

avoid over-diagnosing and over-prescribing with medications that might actually decrease functional abilities.

## ETIOLOGY OF DEPRESSIVE SYNDROMES IN DEMENTIA

There have always been obvious ties between dementia and depressive disorder. Aside from the overlap of symptoms in both illnesses (to be discussed further on) is the suggestion based on findings by a number of groups<sup>9-13</sup> that an earlier psychiatric illness, particularly depression, is a risk factor for Alzheimer's disease. This may be especially important if the depressive episode occurs within two years of the diagnosis of dementia,<sup>14</sup> and might then be considered a "prodrome" of dementia. This is corroborated by prospective work by Reifler et al<sup>15</sup> showing that 40% of 100 older patients with major depression developed a dementia a few years later. These findings may hold true with depressive symptoms<sup>16,17</sup> as well as depressive disorder but may not be apparent, especially if the follow-up period is short.<sup>18</sup>

Reasons put forward for the development of depressive syndromes in dementia are primarily biological ones, such as the depletion of neurons in the locus ceruleus<sup>19-21</sup> or in the central superior (raphe) nucleolus.<sup>20</sup> Another possibility accounting for an association between depression and dementia might be secondary effects on the hippocampus from pathologic over-secretion of glucocorticoids during episodes of severe depression (see critical review by Sapolsky<sup>22</sup>), leading to an increase in the dementia prevalence later.

### Types of clinical presentations in dementia with prominent depressive features (Table 1)

The term "depression" in dementia can be used in describing a variety of situations: an isolated symptom (either consistent or fluctuant), an ingrained pattern of mood and behaviour (either new, or predating the dementia), a normal response to adverse circumstances such as a bereavement, or a major psychiatric disorder such as depressive disorder or bipolar disorder (depressed phase). Depressive symptoms are a normal part of life and although they might occur more frequently in specific clinical situations, by themselves their presence does not necessarily imply that the person has a depressive disorder. We summarize here some of the clinical presentations seen that have significant depressive features.

**Table 1:** Types of clinical presentations in dementia with depressive features

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- Depressive symptoms not fulfilling criteria for specific syndromes
  - Personality changes (such as apathy and passivity)
  - Emotional lability and pathological laughing and crying (emotional dysregulation)
  - Grieving
  - Dysthymia (depressive symptoms less severe than depressive illness and present for at least two years)
  - Major depressive disorder
  - Bipolar disorder, depressed phase
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*Depressive symptoms*

Depressive syndromes insufficient to meet the criteria for major mood disorder by DSM-IV (sub-syndromal depression), are often associated with dementia and are more common than typical major depressive disorder. Burns et al<sup>23</sup> found that of 178 patients with Alzheimer's disease, 63% had at least one depressive symptom, 43% were considered depressed by their relatives but only 24% were rated as being depressed by trained researchers.

The degree of cognitive impairment affects the clinical expression and possibly the frequency of depressive symptoms.<sup>24-30</sup> For example, depression rating instruments that measure a greater number of somatic items achieve higher depression rates in more demented patients, whereas instruments assessing subjective complaints pick up less information in this group.<sup>31</sup> In the most severely demented, caregiver information is generally more likely to identify depression than self-report.<sup>23</sup>

Very subtle depressive symptoms, such as reduction of motivation and interest may present before the clinical diagnosis of dementia is made. Jost and Grossberg<sup>17</sup> found that 72% of patients experienced depression, changes in mood, social withdrawal and suicidal ideation more than two years before the diagnosis of dementia.

A possible factor facilitating the expression of depressive symptoms in early dementia is the retention of insight into cognitive deterioration,<sup>9,24,32</sup> although contradictory evidence in this regard has been published.<sup>33-35</sup> Bungener et al<sup>36</sup> found that loss of control was a significant factor for the development of depressive symptoms and it would seem intuitive that remaining awareness of increasing cognitive deficits might interact with gradual loss of autonomy and control to cause demoralization.

*Personality changes (such as apathy and passivity)*

Personality change, particularly increasing apathy and passivity, is an integral part of the dementing process and is a frequent concern of families of cognitively impaired patients. Apathy is clearly a separate entity from depression, yet families frequently interpret it as depression and request intervention. Marin<sup>37</sup> describes apathy as involving at least three deficits of psychological functioning: 1.) diminished, overt, goal-directed behaviour; 2.) paucity of goal directed thinking; and 3.) attenuation of a person's emotional responses to goal-directed events. These deficits can significantly worsen independent functioning of demented patients and cause increased caregiver burden.

Apathy can also be seen as a "negative symptom", i.e. an absence of a normally present attribute, rather than an additional symptom like a delusion and researchers, such as Galynker et al,<sup>38</sup> have found that negative symptoms increase with the degree

of cognitive impairment, unlike classical depression scores (such as the Hamilton Depression Rating Scale), suggesting that the development of negative symptoms is not related to depression.

Apathy can occur in a variety of disorders, including white matter disease, basal ganglia disorders and schizophrenia, as well as in cortical dementia.<sup>39-42</sup> Some selective serotonin reuptake inhibitors (SSRIs)<sup>43-45</sup> or neuroleptics may themselves cause apathy.

There are some suggestions for pharmacotherapeutic management of apathy in dementia<sup>37,46</sup> but the quality of the evidence regarding its efficacy is not strong and most treatments have significant adverse effects in frail, demented people. As a result, the authors have not made definitive pharmacological recommendations and would suggest (on clinical experience) that the first line of intervention is to provide increased structure for the person, such as a day program with programmed activities. Clinicians interested in reviewing further biological treatments might read studies on stimulants,<sup>38,47</sup> cognitive enhancers such as tacrine<sup>48</sup> or metrifonate,<sup>49</sup> anti-Parkinsonian medications in various brain disorders,<sup>37,50,51</sup> low dose risperidone,<sup>52</sup> bupropion,<sup>37</sup> or L-Deprenyl.<sup>53,54</sup>

*Emotional lability and pathological laughing and crying ("emotional dysregulation")*

Abnormal mood and affect are not uncommon in dementia and are described by a variety of names, such as pathologic affect, emotional lability, emotional incontinence, or pathological laughing and crying. These entities are all types of emotional or affective dysregulation<sup>55</sup> and are often seen in disorders affecting the central nervous system. Although more frequent in vascular dementia<sup>56</sup> and in other subcortical disorders, they are also found in 30% of patients with mild to severe Alzheimer's disease and are often associated with other psychiatric symptoms such as anxiety, depressed appearance, increased activity and aggression.<sup>57</sup> Women appear to be more vulnerable to this dysregulation.<sup>58</sup> When severe, symptoms can be extremely upsetting to families, caregivers and co-patients, especially if they don't understand their origin.

Aside from depressive disorder, which generally involves more sustained symptoms, possible differential diagnoses include essential crying, which is a life-long tendency to cry easily, or the less common interictal crying in some seizure disorders.

Risk factors for emotional dysregulation include specific CNS lesions,<sup>59-60</sup> family history of depression and subcortical atrophy,<sup>61</sup> hormonal factors,<sup>62</sup> cholinergic factors<sup>63</sup> and possibly even more advanced stages of cognitive impairment.<sup>64</sup>

Although a few DBPC studies are reported,<sup>65-68</sup> summarized

**Table 2:** Double-blind placebo controlled treatment studies of emotional dysregulation cited in Arciniegas and Topkoff<sup>55</sup>

Agent	Cognitive disorder	Result	Reference
Imipramine	Stroke or hypertensive disease	Some improvement but small N	Lawson and MacLeod, 1969 <sup>67</sup>
Nomifensine	Multiple sclerosis	8/12 responded well (small N)	Schiffer et al, 1985 <sup>66</sup>
Citalopram	Stroke	N=16, rapid improvement in most	Anderson et al, 1993 <sup>68</sup>
Nortriptyline	Stroke	All significantly improved, N=28	Robinson et al, 1993 <sup>65</sup>

**Table 3:** Double-blind placebo controlled treatment studies of dysthymia in older adults

Agent	Cognitive disorder	Result	Reference
Paroxetine	None noted	N=211, moderate efficacy compared to placebo	Williams et al, 2000 <sup>73</sup>
Acetyl-L-Carnitine	None noted	Acetyl-L-Carnitine > placebo efficacy	Bella et al, 1990 <sup>74</sup>

In Table 2, most data on pharmacological treatment come from case reports and case series and suggests that patients with emotional lability or pathological laughing and crying may variably respond to antidepressants, mood stabilizers, anti-Parkinsonian agents or even stimulants.<sup>55</sup> The mechanism of action of these interventions is likely different from the action in depression, as the improvement has been noted to be independent of other depressive symptoms.<sup>65,66</sup>

In summary, there is some support for pharmacological treatment in emotional dysregulation but, due to the paucity of data, clinical suggestions are to consider treatment only in the more severe presentations.

#### Grieving

Losses are increasingly a part of older people's lives and may be particularly difficult in the cognitively impaired senior with impaired coping skills who may have relied on their spouse, for example, to manage their more complex demands. Grief symptoms in all stages of life are normal and cannot be dealt with by simple pharmacotherapy alone. However, difficulties differentiating between normal grief and depressive disorders are not uncommon, due to the overlapping symptoms, and pharmacotherapy might be cautiously attempted in the case of a grieving senior whose symptoms are continuing to worsen after a period of a few months, as depressive disorder might be precipitated by a bereavement.

#### Dysthymia

Dysthymia in the elderly appears to be less common than in the young, has less associated psychiatric comorbidity but closer links to severe life stresses, particularly medical illnesses.<sup>69</sup> Unlike in younger patients, older women and men are equally likely to develop dysthymia, which tends to present initially in middle years (mean 55.2 years in Devanand et al's study<sup>70</sup>). However, dysthymia may have significant adverse effects on life in demented as well as in nondemented seniors. High dysthymia rates in dementia have been reported: Bungener et al<sup>36</sup> found a dysthymia rate of 8% in her neurology clinic sample of 118 patients with Alzheimer's disease and Migliorelli et al<sup>24</sup> cite a dysthymia rate of 28% of 103 patients from their neurology outpatient clinic (a very select group of patients). Migliorelli's group found that dysthymia was most pronounced early in the course of dementia and was correlated with a greater patient awareness of cognitive deficits.

In the younger adult population, there is well-documented support for the successful pharmacological treatment of dysthymia.<sup>71</sup> Treatment of dysthymia in the general elderly population<sup>72</sup> also appears to be effective in various open label studies and two available DBPC trials (see Table 3), so it seems reasonable to consider cautious treatment initiation even in this demented elderly subgroup.

#### Major depressive disorder

Major depressive disorder can occur at all stages of a dementing illness and, except in the latest stages of dementia, presents with similar signs and symptoms as depression without dementia.<sup>8</sup> Its prevalence of occurrence is likely stable throughout the course of dementia,<sup>24</sup> although, as with the lesser depressive syndromes above, contradictory reports cite both decreases<sup>75</sup> and increases<sup>30,76</sup> with the worsening of cognitive impairment. The cited prevalence varies widely, which may reflect differences in the sample populations or diagnostic approaches: Wragg and Jeste<sup>77</sup> review the literature and find prevalence rates of 10-20%, although some authors, such as Bungener et al<sup>36</sup> find that not one out of 118 patients in their neurology clinic sample had a major depressive disorder. Recent studies continue to embody this variability, depending on the methodology (and rating scale) used.<sup>78,79</sup> For example, Brodaty and Luscombe<sup>80</sup> show that among their sample of 288 outpatients with dementia, the following depression prevalence rates were found by scale: Hamilton Rating Scale for depression - 7.4%, Geriatric Depression Scale - 8%, DSMIV - 6.3%.

Risk factors for the development of depression in demented people include a past history of depression,<sup>79,81</sup> a family history of depression,<sup>81,82</sup> the early onset of dementia and female gender.<sup>15,76,83</sup> Depression is more common in vascular dementia than in Alzheimer disease.<sup>84</sup>

Treatment of depressive disorder in dementia is discussed later on.

**Table 4:** Sig:E Caps: A Mnemonic for Symptoms of Major Depression and Dysthymia.

- Sleep disorder (either increased or decreased sleep)\*.
- Interest deficit (anhedonia).
- Guilt (worthlessness,\* hopelessness,\* regret).
- Energy deficit\*.
- Concentration deficit\*.
- Appetite disorder (either decreased or increased)\*.
- Psychomotor retardation or agitation.
- Suicidality.

\* NOTE: To meet the diagnosis of major depression, a patient must have four of the symptoms plus depressed mood or anhedonia, for at least two weeks. To meet the diagnosis of dysthymic disorder, a patient must have two of the six symptoms marked with an asterisk, plus depression, for at least two years.

Sig:E Caps=SIG + Energy + CAPSules

*Bipolar disorder, depressed phase*

Bipolar disorder is not common in old age but may be encountered, even in the absence of a previous history. Late onset bipolar disorders can result in very severe depressive episodes requiring electroconvulsive therapy (ECT). Treatment must be undertaken cautiously, as antidepressants may precipitate a mania (which can mimic severe agitation or anxiety), or cause rapid cycling, which, superimposed on dementia, can be difficult to manage.

**Evaluation and diagnostic difficulties**

Standard mnemonics such as Sig:E Caps (see Table 4) for reviewing the core symptoms of depression are helpful to physicians but must be qualified in more complex populations such as in the demented elderly. The diagnosis of depression in the elderly without dementia is already more complicated: the NIH Consensus Development Panel<sup>85</sup> reviews this issue citing a variety of reasons including ageist assumptions, comorbidity with other medical illnesses and heterogeneous presentations, among others. In the demented elderly, there are even more challenges, as noted below.

**Overlapping symptoms**

The most challenging problem in the separation of mood from cognitive disorders is the overlap of symptoms. These include cognitive changes, weight loss, sleep changes, expressions of sadness or demoralization, irritability and loss of interest, or apathy. Each of those symptoms, although occurring in both illnesses, has a different characteristic clinical pattern that can help to distinguish its etiology (see Appendix I).

It is known that depressive illness is often accompanied by various cognitive deficits which are generally reversible with the resolution of the illness. Treatment of a depressive illness with anticholinergic antidepressants (even at low serum anticholinergic levels) can further worsen cognition.<sup>86</sup> Mild deficits might be seen in secondary memory, verbal fluency, visuospatial skill, novel problem solving and sustained attention,<sup>87</sup> as well as in executive function and functional ability.<sup>88</sup> Most importantly though, while both demented people and depressed people often score poorly on cognitive and functional measures, those with just dementia often volunteer incorrect information and answers and appear undisturbed by this, whereas depressed people are more concerned about their actual (and perceived) deficits than seems appropriate.

Weight loss is a hallmark of depressive illness (said by some<sup>89</sup> to be the most common cause of weight loss in the nursing home) but it is also a feature of dementia alone.<sup>90</sup> The reasons for this are not completely clear and may not only be due to “forgetting to eat” but other, as yet undefined factors. Weight loss in depression tends to be more “subacute” i.e. occurring over the course of weeks, rather than months or years.

Sleep changes are typical of depression and dementia. In dementia the sleep changes are due to a slow and gradual loss of diurnal rhythms, whereas in depression there is a subacute change: either an increase or a decrease over the course of weeks, most typically as intermittent night-time waking and terminal insomnia. Electroencephalographic sleep data show differences between depressed patients and demented patients,<sup>91</sup> but in practice these data are not usually available.

Irritability can occur in both dementia and depression. In dementia this usually occurs in the middle to later stages, when significant cognitive impairment is already present. However, if a patient with dementia develops increased irritability subacutely, accompanied by changes in sleep and appetite, the diagnosis of depression superimposed on dementia is likely.

Ill-defined feelings of sadness and lack of interest are not uncommon in the early stages of dementia, as discussed in the section above on specific depressive syndromes. If this becomes consistent and gradually more severe over the course of a few weeks, however, the possibility of a superimposed depression must also be considered.

**Communication difficulties**

Clearly, most psychiatric diagnoses rely heavily on the patient's ability to communicate symptoms and feelings. Making a diagnosis of depression in a poorly communicative dementing person is very difficult and requires more lengthy interviewing of caregivers as well as the careful observation of behaviours. Clinician bias both for, or against, depression can also adversely influence the accurate detection of clinical syndromes.

**Psychological insightfulness**

Even in elderly patients with intact language, the ability to describe psychological symptoms is less than in the currently young, as the necessary vocabulary may never have developed. This can be exacerbated with progressive cognitive deterioration.

**Ageist assumptions**

Many younger people assume that the quality of life in older people, especially in those with significant cognitive disabilities, is poor and that it is natural to have depressive symptoms in these cases. Some therefore feel that even suicidal behaviours are logical and interventions are unwarranted. Even demented people with obvious depression are thus often untreated, leaving them with much needless suffering.

**ASSESSMENT TOOLS**

Although standard depression tools have been used in the assessment of depression in dementia, difficulties in their application led to the development of specialized scales for use in dementia. The most widely used are the Cornell Scale for Depression in Dementia<sup>92</sup> and the Dementia Mood Assessment Scale.<sup>93</sup> Both these scales are easy to use and have focussed on signs that are easy to rate in cognitively impaired people and that have a high correlation to the diagnosis of depressive disorder. Other scales such as the Depressive Signs Scale<sup>94</sup> and Greenwald and Kramer's Gestalt rating of depression in advanced dementia<sup>95</sup> have also been found useful by some. Jacobs et al<sup>96</sup> also described the successful application of the CERAD Behaviour Rating Scale<sup>97-99</sup> to separate depressed from nondepressed demented people, although this scale requires more training and time than, for example, the Cornell scale. In general, the scales described are only screens and not a replacement for a full assessment by a clinician skilled in dealing with persons with dementia. They are, however, useful in suggesting likely mood disorder and might help in identifying previously missed depressed people.

Neuroimaging and electroencephalographic data might

eventually be helpful in differentiating between dementia and depression but this work is in early stages.<sup>91,100-105</sup>

Currently, the best gold standard for differentiating dementia with associated mood changes from depressive illness or the various depressive syndromes is a careful assessment of past history, family history, symptom type (see earlier) and temporal course (see Appendix I). In some cases doubt will remain as to the diagnosis and careful trials of medications with longitudinal follow-up are a reasonable option.

#### NONBIOLOGICAL TREATMENT

Nonbiological interventions are important as adjuncts to medical management but can also stand alone, especially in the less “biological” depressive syndromes such as reactive depressive symptoms in early dementia. Teri<sup>106,107</sup> believes that aversive events and interactions can perpetuate depression in dementia and describes strategies to alter aversive events and to increase pleasant interactions. Adjusting the caregiver’s expectations to a more realistic level and thus decreasing both patient and caregiver frustration can also be very helpful. The tendency to personalize difficult behaviours and to attribute them to deliberate maliciousness can be reduced with education and support.

The support of caregivers is very important, as their rate of stress and psychiatric symptomatology is considerable,<sup>108</sup> leading to a greater use of psychotropic medications in the caregivers<sup>109</sup> and often becoming a key issue in the decision to institutionalize. Family interventions may slightly delay institutionalization of the patient<sup>110-112</sup> as well as improve the caregiver’s quality of life, although significant reductions in health care utilization for the caregiver are less robust.<sup>113</sup>

Various therapies have been used in different stages of the dementing process. These include counselling, individual and group insight-oriented psychotherapy, life review and reminiscence therapy, cognitive therapy, problem solving therapy, behaviour therapy, relaxation techniques and family therapy.<sup>114-115</sup> Although difficult to evaluate objectively in a DBPC fashion, many of these interventions may have positive impact at a variety of levels.

#### BIOLOGICAL TREATMENTS

With some exceptions,<sup>116</sup> the literature suggests that response to the treatment of depressive illness in dementia appears to be less robust<sup>117-118</sup> than that in patients with uncomplicated depression, consistent with the Alexopoulos<sup>119</sup> study associating enlarged lateral ventricles with poor response to tricyclics. More severe dementia may be associated with even poorer prognosis.<sup>120</sup>

Available treatment studies of depression in dementia are hard to compare, as the diagnostic categories described vary from negative symptoms of dementia to classical depressive illness superimposed on dementia. Furthermore, although there are case reports and case series, reports of the use of antidepressants to treat depressive syndromes in people with dementia, chart review type publications and a few open prospective trials, there are fewer DBPC studies,<sup>121-127</sup> or randomly allocated depression treatment comparison studies. Placebo response has been found to be particularly high in this

group,<sup>118,121</sup> so it is very important that recommendations of specific efficacy base its comments on placebo controlled studies. In Table 5, we summarize briefly the few DBPC studies on patients with reasonably well-defined criteria for dementia and depressive syndromes.

In general, recent meta-analyses of depression treatment in geriatric patients have concluded that no individual antidepressant is clearly more effective,<sup>128</sup> and that the clinical use of a particular antidepressant should be guided by current rational prescribing approaches in the nondemented elderly. Table 6 reviews general issues of drug treatment of depression in the elderly (see<sup>129</sup>).

In summary, issues such as changes in pharmacodynamics and pharmacokinetics must be considered, as should other effects such as anticholinergic action, postural hypotension, arrhythmias and drug-drug interactions. In patients with dementia, there is increased vulnerability to many of these, especially the anticholinergic effects,<sup>121,130</sup> with noticeable but subtle cognitive decrements occurring from even low doses (25 mg per day) of agents such as imipramine in depressed Alzheimer patients.<sup>131</sup> This effect is comparatively less problematic with the SSRIs,<sup>132</sup> although these drugs are not free of adverse effects in the elderly.

In spite of various adverse effects of pharmacological treatment, clinical improvement of significant depression in a demented patient might result in improved memory functioning,<sup>133</sup> and general functional improvement.<sup>134</sup>

ECT has been found by various authors to be successful in people with dementia and depression, most recently Rao and Lyketsos,<sup>135</sup> in a retrospective study. In the most severe depression, ECT is the most effective and quickest treatment, especially for those patients who have stopped eating and drinking, who are suicidal, severely distressed, or who have psychotic features. ECT generally does not cause permanent cognitive deficits but can cause a temporary increase in confusion during the treatment course. Ethical dilemmas may arise, as families of severely demented patients often specify that no extraordinary measures be employed and ECT is perceived as more extraordinary than antidepressants. There are also remaining negative emotional societal (and medical) responses to ECT, which may result in the refusal of this highly successful, potentially life-saving treatment option.

#### CONSENSUS RECOMMENDATIONS

Other organizations have published guidelines for the treatment of depression in dementia, such as those within the American Psychiatric Association Practice Guidelines,<sup>136</sup> and from within the joint guidelines of the more multidisciplinary group comprised of the American Association for Geriatric Psychiatry, the Alzheimer’s Association and the American Geriatrics Society.<sup>137</sup> Guidelines from a single professional group tend to be more specific and perhaps controversial than those hammered out in a heterogeneous group with differing clinical experiences. For example, geriatric psychiatrists tend to be stronger advocates of ECT in the depressed elderly, as they are more likely to be familiar with severe, life-threatening depression that has responded well to this.

An important benefit of the large, heterogeneous group

**Table 5:** Double-blind, placebo controlled studies of depressive disorder in dementia

Agent	Population	Methodology/Instruments	Results	Other comments
Imipramine Reifler et al, 1989 <sup>121</sup>	61 patients with DAT and major depression (N=28) or without major depression (N=33)	8 weeks, HamD response, MMSE, OARS, imipramine in therapeutic range in treatment group	Depression improved comparably on imipramine and placebo, those on imipramine worsened more on the Dementia Rating Scale.	Anticholinergic effects likely adversely affected the cognition of the imipramine group.
Clomipramine Petracca et al, 1996 <sup>122</sup>	24 neurology outpatients with DAT and either DSMIII-R criteria of major depression or dysthymia; HDS > 10	HamD, MMSE, FIM	Both groups improved, but clomipramine patients achieved lower acute HamD scores; MMSE score improved more during clomipramine cross-over to placebo, suggesting more adverse cognitive effect.	No clomipramine improvement on activities of daily life, improvement of depression on clomipramine
Moclobemide Roth et al, 1996 <sup>123</sup>	I. Dementia with depression (DSM-III-R) and HamD >14 (N=511) II. Major depression with cognitive impairment (N=183)	6 weeks moclobemide or placebo; HamD, MMSE, SCAG, GDS, others	Both groups showed decreased HamD scores, but more so in both moclobemide groups.	No adverse effects from moclobemide
Citalopram Gottfries et al, 1992 <sup>124</sup>	149 in- or outpatients with mild to moderate dementia and/or somatic disorders, with 29 patients having both depressive illness and dementia, DSM-III criteria	6 week DBPC trial. Ratings: GBS scale, HRSD, CGI, MADRS	Cognitive and emotional improvement in the demented patients on citalopram and depressive symptoms improved in both the depressed and the nondepressed groups.	Findings hard to interpret because of heterogeneity of patient groups which had various combinations of dementia and depression or neither.
Sertraline Lyketsos, 2000 <sup>125</sup>	22 outpatients with DAT	12 week DBPC, response by Cornell Depression Scale decline, HamD, MMSE	Significantly more symptom decline for sertraline than placebo; more at least partial responders on sertraline.	
Sertraline Magai et al, 2000 <sup>126</sup>	31 female nursing home patients with severe DAT and either minor or major depression	8 week DBPC study; measures: MMSE, BCRS, FAST, Global Deterioration Scale (stages 6,7), Cornell Scale >or=3, Gestalt scale > or =1.	Both groups improved, but only the clinical "knit brow" measure approached statistical significance.	<ul style="list-style-type: none"> <li>• Inconclusive but interesting study.</li> <li>• Difficulty in rating depression in severely demented patients</li> <li>• Visual ratings may be of use.</li> </ul>
Maprotiline Fuchs et al, 1993 <sup>127</sup>	DSMIII-R dementia and mild depression (290.1, "not requiring antidepressant therapy")	Clinical video rating of overall improvement, Geriatric Depression Scale (GDS)	No improvement of maprotiline on clinical rating, maprotiline better than placebo on GDS (P=0.09).	Inconclusive study possibly due to mild depressive symptoms in study group

Dementia, Alzheimer's type (DAT); Hamilton Depression Rating Scale (HamD); Global Depression Scale (GDS); Mini-Mental State Examination (MMSE); Older Americans Resources and Services Activity of Daily Living Scale (OARS); Functional Independence Measure (FIM); Sandoz Clinical Assessment Geriatric Scale (SCAG); Geriatric Depression Scale (GDS); double-blind, placebo-controlled (DBPC); Gottfries-Bane-Steen (GBS); Clinical Global Impression (CGI); Montgomery Asberg Depression Rating Scale (MADRS); Brief Cognitive Rating Scale (BCRS); Functional Assessment Staging (FAST)

**Table 6:** General clinical issues influencing drug treatment of depression in the elderly

Clinical Issues	General Recommendations/ Impact*
Decreased hepatic metabolism (small effect on most antidepressants) Pharmacodynamic changes less clear but frequently increased end organ increased response to adverse effects.	Lower initial dosing of antidepressants with gradual upward titration
Higher percentage of total body fat, wider distribution of lipid soluble drugs and longer half-life (particularly for anxiolytics and antipsychotics).	Minimize the use of anxiolytics and hypnotics, especially those with long half-life
Reduction of renal function and clearance of drugs (particularly lithium and gabapentin)	Start renally excreted drugs at very low doses and adjust according to blood levels.
Higher likelihood of adverse effects of all kinds.	Monitor more closely for side effects.
Higher prevalence of osteoporosis, cardiac problems, postural instability, cognitive impairment and other medical vulnerabilities.	In general, choose drugs less likely to cause cardiovascular or anticholinergic side effects. Tricyclic antidepressants (TCAs) are not usually first line choice as more likely to worsen most common medical problems found in the elderly. If TCAs are used, secondary amines such as desipramine and nortriptyline should be preferred. Specific choice is guided by medical vulnerabilities and drug interaction profile.
Increased duration of depressive episodes with age.	Longer recommended active treatment time (2 years).

\* Not presented at consensus meeting, added after reviewer comments.  
Tricyclic antidepressants (TCAs)

**Table 7:** Clinical information guiding choice of treatment of depressive disorder in dementia\*

Intervention category	Specific intervention	Effectiveness	Cautions
Pharmacological	Tricyclic or heterocyclic	Effective, although slightly less so than in depression without dementia. Possibly more effective than SSRIs in chronic pain.	Anticholinergic (may worsen cognition), postural hypotension, arrhythmias, lethal in overdose. Nortriptyline, desipramine relatively better choices.
	SSRIs, Citalopram,	Effective, <i>possibly</i> less so than TCAs	Stimulation, agitation, GI effects, SIADH, (Fluoxetine has very long half-life)
	Nefazodone	in very severe depression.	
	Trazadone	Requires high doses for major depressive disorder	Sedating (helps with agitation) but postural hypotension can be a problem
	Moclobamide	Effective	Possible stimulation
	Serotonin norepinephrine reuptake inhibitor	No studies available in dementia but likely effective based on general population data. Possibly also effective in chronic pain	Similar to selective serotonin reuptake inhibitors, may cause hypertension
	Bupropion	No studies available in dementia but possibly effective based on general population data	Not to be used in eating or seizure disorders based on younger patient studies
Other biological treatments	Electroconvulsive therapy	Effective, particularly in severe depression and psychotic depression	Some short-term confusion, anaesthetic risks
Psycho-social	Psychological and other	Probably helpful as an adjuvant therapy	Need to be tailored to the cognitive capabilities of the patient

\*Recommendations by Thorpe/Groulx, not part of consensus process, mostly clinical opinion level evidence  
Tricyclic antidepressants (TCAs); Gastro-intestinal (GI); Syndrome of inappropriate ADH secretion (SIADH)

**Table 8:** Consensus recommendations for the treatment of depressive syndromes in dementia

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- a. As depressive syndromes are common in patients with dementia, physicians should consider diagnosing depression when presented with the subacute (i.e. weeks, rather than months to years) development of symptoms characteristic of depression such as behavioural symptoms, weight and sleep changes, sadness, crying, suicidal statements or excessive guilt. (Grade B, Level 3, consensus)\*
- b. Depressive illness in dementia should be treated and when refractory, referral should be made to an appropriate specialist\*\*. (Grade B, Level 3, consensus)
- c. Depressive symptoms that are not part of a major affective disorder, severe dysthymia or severe emotional lability should initially be treated nonpharmacologically. (Grade B, Level 3, consensus)
- d. In patients suffering from disturbing emotional lability or pathological laughing and crying, consider a trial of an antidepressant or a mood stabilizer. (Grade B, Level 3, consensus)
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\*This is not meant to imply that depression lasting for a long time should not be treated but that symptoms of sleep, appetite and weight change, for example, which have developed subacutely, should trigger a high index of suspicion for the presence of depression. (Added after reviewers' comments, not from consensus committee discussions)

\*\*Preferably a geropsychiatrist, if available

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developing consensus statements, though, is that leading professionals in various fields subject their knowledge base and opinions to a wider group, receiving valuable input and possibly even challenging firmly held but academically shaky beliefs. Opinion leaders participating in the consensus process may then influence their respective disciplines, improving the general knowledge base in the area.

The fairly general consensus guidelines on the treatment of depressive syndromes in dementia (Table 8) presented here, reflect the averaging process of a large multidisciplinary group but also the somewhat shaky evidence base of the treatment of depression in dementia, especially the less classical presentations, such as emotional lability. Clinicians working with the demented elderly have a strong consensus that depression in dementia is an important problem which often requires intervention but have a harder time making specific and strong recommendations.

## CONCLUSIONS

Depressive syndromes are common in dementia and may be integral aspects of its natural development. The treatment of each syndrome varies, as does the successfulness of the intervention.

The treatment of depressive illness in particular needs to adhere to the general guidelines for antidepressant management of the elderly person, to insure the prevention of further cognitive and other functional disability. The trend of the current literature is to support the efficacy, albeit slightly reduced, of the usual antidepressants that are clinically useful in the general geriatric population. First line agents likely should be the non-tricyclics due to their general lack of anticholinergic effects, although geriatric clinical experience still finds the tricyclics helpful at times. It is clear that the treatment of serious depressions in dementia will improve the functional status overall, even with some anticholinergic effects but treatment decisions will remain difficult in milder depressions where the risk-benefit ratio is less clear. Not to be forgotten in severe cases, is the use of ECT, which, in spite of its bad publicity, is still the most effective and rapid treatment, which can save lives.

Of interest in the future and in need of further study, is the possibility of the so-called cognitive enhancers improving the less classical depressive symptoms interwoven with dementia. Other interventions for mood symptoms not classical of major depressive illness such as mood stabilizers, stimulants, ginkgo biloba and dopaminergic medications also need further study. Finally, it is crucial to remember that nonpharmacological interventions can improve the quality of life of demented patients, ameliorate the less classical depressive syndromes and help families cope better with their stressful task.

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**Appendix I: General clinical guide to distinguishing depressive disorders from dementia.**

<b>Category</b>		<b>Depressive illness</b>	<b>Dementia</b>
<b>General</b>	Onset of symptoms Progression Diurnal pattern	Can usually be dated to within a few weeks Subacute (weeks to months) Symptoms generally worst in morning	Very insidious Slowly (months to years) Generally worst in evening (“sundowning”)
<b>Somatic symptoms</b>	Sleep Appetite/weight Energy Activity	Subacute (weeks to months) development of early morning wakening, intermittent night-time wakening Subacute decrease of appetite and weight Subacute decrease Generally decreased but may be increased in agitated depression	Gradual loss of diurnal sleep wake patterns Gradual loss of weight may occur Gradual loss of activity mostly related to apathy Increased or decreased, often most noticeable in the late afternoon or evening (“sundowning”)
<b>Mood symptoms</b>	Mood Affect Crying Guilt Suicidal thoughts or plans Lack of interest Complaintiveness Self image	Subacute onset of sad mood, pervasively present every day for at least a few weeks Sad to severely flattened, developed subacutely Without obvious reasons, consistent with low mood Often present Moderately frequent Subacute onset Newly developed over a few weeks, stable Very poor, out of context to deficits	Fluctuant, episodic sad mood may be present Flattened gradually Episodic, labile, often in response to a stressor, may be interspersed with normal mood episodes Rarely present Infrequent Chronic development May be intermittently present Usually good, sometimes inappropriate self-assessment
<b>Psychotic symptoms</b>	Hallucinations Delusions	Mostly auditory, mood congruent (i.e. negative flavour), associated with severe depression Negative in flavour, associated with severe depression and mood congruent	Visual most common, variable content, episodic, usually occur in later part of dementing illness Paranoid most common, present even in normal mood periods
<b>Cognitive changes</b>	Memory Testing results Insight Attention/concentration	May be impaired, subacutely, during depressive episode Variable Excessive focus on perceived deficits and excessive concern Often normal	Consistently impaired Consistently poor Frequent minimization with lack of appropriate concern Often abnormal
<b>Examination</b>	General presentation Primitive reflexes Apraxia/agnosia	Patient in distress and suffering, interviewer may perceive the interview as “depressing” Normal Absent	Often unconcerned and in little distress Abnormal in later stages Often present
<b>Family history</b>	Depression Dementia	Often present	Often present