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Prognosis of depression in the elderly in comparison with adult age. Is there a significant clinical difference?

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Major depressive disorder is typically a chronic disorder in which the chances of suffering a single non-recurring episode are low. To date it has been uncertain how «age» moderates prognosis. It has been especially difficult to separate the effect of age of first episode onset from the overall effect of age at the time of recruitment. From a methodological perspective, this question is best studied in inception cohort studies rather than naturalistic studies. In inception cohort studies, all patients receive treatment under controlled conditions and therefore the effect of age (if any) may be more apparent. In addition, the best evidence comes from comparative studies which have examined older and middle aged patients within the same study.

After conducting a thorough review of the literature, we have found three comparative inception cohort studies of episode remission in older versus middle aged patients. We found only one comparative inception cohort study of relapse and recurrence in older versus middle aged patients. This evidence suggests that depression in the elderly (those of older chronological age) responds equally to the initial treatment but has a more adverse longitudinal trajectory than depression in middle age. An early age of illness onset also seems to adversely affect prognosis in comparison to those with a first onset in later life who do not have medical comorbidity. The effect of age on prognosis may be largely explained by factors such as previous episodes and medical comorbidity.

Key words:
Depression. Prognosis. Age of onset. Late onset.

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Pronóstico de la depresión en la tercera edad en comparación con la edad adulta. ¿Existe una diferencia clínica significativa

La depresión mayor es típicamente un trastorno crónico en el cual la probabilidad de sufrir un solo episodio no recurrente es muy baja. Hasta el momento ha permanecido incierto cómo el factor «edad» modera el pronóstico. Especialmente ha sido difícil separar el efecto de la edad de comienzo de la enfermedad del efecto global de la edad en el momento de inclusión o reclutamiento para los estudios. Desde un punto de vista metodológico esta cuestión se estudia mejor mediante estudios incidentes (*inception cohort studies*) que mediante estudios naturalísticos (*naturalistic studies*). En los estudios incidentes todos los pacientes reciben tratamiento bajo condiciones controladas y, por tanto, los efectos del factor edad (si existe alguno) pueden ser más aparentes. También la mejor evidencia se consigue a través de estudios comparativos que examinen pacientes de la tercera edad y de la edad adulta más joven en el mismo estudio.

Tras haber llevado a cabo una exhaustiva revisión de la literatura hemos encontrado tres estudios de episodios de remisión en pacientes en la tercera edad en comparación con la edad adulta más joven, comparativos y de incidencia. Sólo hemos encontrado uno, comparativo y de incidencia, de recaída y recurrencia en pacientes de tercera edad en comparación con edad adulta más joven. Éstos sugieren que la depresión en la tercera edad (refiriéndonos a la edad cronológica) responde igualmente al tratamiento inicial, si bien, presenta una trayectoria longitudinal más adversa que la depresión en la edad adulta más joven. La presencia de una edad más temprana de comienzo de la enfermedad también parece afectar de manera adversa al pronóstico en comparación con el comienzo en edad más avanzada, esto es, en aquellos pacientes que no presentan comorbilidad médica. El efecto de la edad en el pronóstico podría explicarse fundamentalmente por factores como la presencia de episodios previos y la comorbilidad médica.

Palabras clave:
Depresión. Pronóstico. Edad de comienzo. Tercera edad.

INTRODUCTION

There is generalized consensus among clinical specialists that the chances that an individual who has suffered an episode of major depression has a high likelihood of suffering another episode. A large group of independent works in the 1950's and 1960's presented graphic data on remission, including relapses and recurrences (table 1).[1] According to studies based on samples of patients with depression during the elderly age, the risk of recurrence is at least 50% during the two years post-treatment.[2] Similar findings were reproduced in a recent study that examined the modern concept of «natural history» of depression in the elderly (that is, patients under treatment or follow-up under usual conditions not included within the context of research studies). A 6-year longitudinal study, Aging Study Amsterdam, showed that 44% of depressed patients presented a fluctuating course, 32% experienced a severe chronic course and only 23% achieved a good outcome after reaching remission.[3] Is this adverse course specific to the elderly (or, perhaps «the oldest old»),[4] or do younger adult patients share a similar risk?

Perhaps a clearer understanding of the prognosis of depressions in the early adult age was obtained with the development of large studies in the 1990's.[5-9] In the repeatedly and widely cited National Institute of Mental Health Collaborative Depression Study, 431 participants with Major Depression were subjected to a five-year follow-up. Twelve percent did not recovery prior to the study end and although 50% of the patients achieved remission within a 6 to 12 month period, about half relapsed during the next year.[10] Other longitudinal follow-up naturalist studies have reported relapse/recurrence levels for patients in clinical remission status above 30% in the following year,[11] with a cumulative accumulate recurrence rate of 85% or more after 15 years.[12] Clearly, these mean rates are influenced by several factors. In this context, the most consistent findings are disease duration, episode duration, and number of episodes at the time of initial clinical evaluation.[13-15] In other words, the more persistent the depression at the beginning of the clinical follow-up (at baseline), the higher the likelihood that it will also be persistent in the future. This may mean an increased possibility of relapse of 16% with each new episode,[16] although, in fact, it is very unlikely that this effect of the influence follows a simple linear function. Other chronicity risk factors have been clarified recently by the STAR-D study (table 2).[17] One research group tried to combine risk factors involved in the depression course that affect their outcome, creating a «prognostic index of depression» in the primary care context.[18]

Up to now, the information presented leaves one question unsolved. If the evolution after remission of the depression in both the elderly and adult age shows unfavorable results, the question could be raised if important differences exist regarding prognosis in studies that have been dichotomized or stratified by age. The first thing that we must decide is how we define the variable «age» in relationship to the disease course. For example, is the patient's chronological age when he/she enters into the study also the age at onset of the depressive disease, and finally the age of appearance of the first symptom? The latter is clearly of interest, but it has never been studied in relationship to prognosis, even if it is taken into account that the delay from the appearance of the first symptom until professional help is received is typically eight years.[19] However, the duration of this delay period is related to the disease onset at an earlier age and to an older age at the time of the interview.[20] The studies differ regarding the use of «chronological age» or «disease on-

Table 1 Definition of outcomes in depression

Response	The patient no longer has all of the symptoms but there is evidence of more than minimal symptoms.
Remission	The patient does not meet the syndromic criterion and does not present symptoms or only has minimal symptoms.
Relapse	Return to the total symptomatic picture that occurs during the remission; reemergence of present episode.
Recovery	Extended period of remission, typically during more than four months, that indicates the end of the present episode.
Recurrence	Appearance of a new episode of major depression; it only occurs during recovery.

Table 2 Risk factors for chronic depression according to the STAR-D study

Advanced age
Low education level
Low purchasing power
Unemployment
Concomitant physical diseases
Inferior physical quality of life
Generalized concurrent anxiety disorder
Clinical background of suicide attempts
Ethnic minorities
Treatment in primary care

Gilmer WS, Trivedi MH, Rush AJ, Wisniewski SR, Luther J, Howland RH, Yohanna D, Khan A, Alpert J. Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. Acta Psychiatrica Scandinavica 112 (6): 425-433 DEC 2005.

set age» as prediction factors, there being very few studies that use both concepts (and data).[21] Some studies have shown that there is a lower likelihood of remission in those with older chronological age under drug-therapy or electroconvulsive therapy (ECT).[22-24] Other work groups report that a higher chronological age inversely affects response in adult aged depressed patients to drug therapy.[25-27] Can this be interpreted as the fact that the prognosis is worse in elderly patients compared with younger adult patients? Perhaps, but we have also found results that do not confirm it.[28-29] Studies that directly compare cohorts of elderly patients with depression with adult-aged patients who have received a similar treatment are needed. Two recent reviews have presented mixed evidence on the effect that older age has in relationship with the results of depressive disease.[30-31] Herein, we review the studies that present the most solid evidence, that is, we focus on inception cohort studies instead of naturalistic studies, which are methodologically weaker.

SHORT TERM OUTCOMES: REMISSION OF DEPRESSION EPISODE IN ELDERLY PATIENTS COMPARED WITH YOUNGER ADULT AGED PATIENTS

Three inception cohort studies have been published. O'Connor et al. (2001) studied 253 patients treated with bilaterally applied ECT.[32] The patients were stratified into three groups: 45 years or less, 46 to 64 years and 65 years and older, using the chronological age they had when enrolled in the study, without considering the disease onset age. Although there were no differences between the older and intermediate groups, the latter had a lower response to treatment. Katon et al. (2002) studied 282 patients (105 with age range between 18 and 59 years), and 177 who were 60 years or older at the time of enrolment) in a random and multicenter controlled study, with detailed methodology, of an eleven-week follow-up study of paroxetine, problem solving therapy and placebo.[33] Being a woman less than 60 years of age at the time of enrolment was associated to a better response to paroxetine but not to problem solving therapy. Reynolds et al. (1998), of the Pittsburgh Study of Maintenance Therapies in Late Life Depression group, studied the time to remission and time to relapse in 187 elderly patients (mean age = 67.6, standard deviation = 5.8) with recurrent depressive disease initially during one year and then for three years.[34,35] The patients were divided into two groups, those in whom the depressive disease began at under 60 years of age and in those in whom it began at 60 years or more. The authors performed a controlled analysis of the number of previous depressive episodes, finding that the patients in whom the disease onset occurred prior to 60 years took a mean of 5-6 weeks more to achieve remission than those in whom the disease began in the old age.

LONG-TERM OUTCOMES: RELAPSE AND RECURRENCE IN ELDERLY PATIENTS COMPARED WITH YOUNGER ADULT-AGED PATIENTS

We have found only one inception cohort study. In this ambitious study of acute open and random maintenance treatment, Reynolds et al. (1999),[33] in an extension of the previously mentioned Pittsburgh study, randomly distributed 107 patients to one of four maintenance treatment combinations with nortriptyline, interpersonal psychotherapy or placebo. In order to analyze the results, the patients were divided into two groups, those 60 to 69 years of age (n = 69) and those 70 years or more (n = 38), and their follow-up was three years. The authors also divided the patients based on disease age inception into two groups: 129 participants with disease onset prior to 59 years and 58 participants with disease onset at 60 years or more. There were no differences in the proportion of patients who remitted, recovered or relapsed in the first year, although only combined treatment with nortriptyline and interpersonal psychotherapy prevented their relapse in the aged 70 years or more group. They found that having an older age on entry into the study was associated with a greater likelihood of suffering a relapse at three years.

THE INFLUENCE OF CONFOUNDING FACTORS IN THE COMPARATIVE STUDIES

Psychiatric background and previous treatment

The naturalistic studies that include ECT as treatment should be reviewed carefully because there are several reasons why the clinicians refer patients to ECT based on their age. When the previous psychiatric background is taken into consideration, its effect generally has greater weight than other associated risk factors. Thus, depression at the onset of the adult age is linked to a greater number of past episodes and this predisposes to more unfavorable outcomes.

Medical comorbidity

Many studies show that there is high medical-somatic morbidity (and physical disability) in elderly patients with depression, compared with younger depressed patients (or even with elderly non-depressed patients).[36-38] The evidence herein seems to indicate that the older the patient is when their depressive disease begins, the higher is the possibility of suffering comorbid somatic conditions. It seems that the same relationship exists in relationship to the patient's real age, regardless of onset age of the depressive disease.[39,40] It could be questioned if this concomitant morbidity influences response to treatment or selection of said treatment. We have found extensive documentation that relates brain structural changes with negative results for depression.[41-46]

Furthermore some,[47] but not all[48-50] of the studies suggest that medical comorbidity affects its response to treatment. However, the response of depression to treatment may be influenced by specific medical conditions.[51] One meta-analysis of studies of elderly hospitalized medical patients suggests that depression in this group has a worse response to treatment.[52] Specific conditions such as speech disorders, arthritis and skin problems as well as the presence of cognitive deficits may be related with a worse outcome of the depression.[53,54] However, this statement requires more corroborative research work.

Subtype of depression

Major depression is present in 1% of the elderly population while 3% suffer dysthymia and 8% to 15% have significant symptoms of depression.[55] Thus, the importance of «minor» depression, or depression below the diagnostic threshold is undisputed. Current evidence points to negative therapeutic results even in those depressions that do not meet the diagnostic criterion of major depression. In this sense, several studies have shown that the prognosis is more similar to that of a major depression than of the asymptomatic controls.[3,56] In regards to the group of symptomatic patients who do not fulfill all the criteria (minor depression), the episode persists from six months to one year of follow-up in approximately 50%, although this tends to remit during a longer follow-up period.[57] Unfortunately, prognostic prediction factors in this group have not been duly studied.

DISCUSSION

Major depression disorder is typically a recurrent disease that rarely occurs with a single isolated episode. Even depressions treated in Primary Care Centers tend to be recurrent, chronic and associated to cormorbidity.[11,17,58] A total of 85% of those who have a major depressive episode will have at least one more episode during their life time.[59,60] The possibility that they will be hospitalized in a period of ten year ranges from 30% to 60%.[61] The median number of depression episodes in long term studies is 4%, and 25% have 6 episodes or more.[62] Even after acquiring remission, the psychosocial harm tends to persist, in the same way as the subtle cognitive deficits (minor).[63]

And, however, depression is often overlooked. More specifically, affective disorders are not actively studied in the patients regardless of their age in Primary Care Medicine.[64-66] It is important for the reader to understand that an early age of onset of depressive disease gives the patient more time to experience a subsequent episode of the disease. Furthermore, in many hospitals, individuals with late onset age of depression tend to be treated in a completely different physical-care setting and environment than younger adult patients. The treatment expectations, and the treatment itself offered, will very likely be different from that of younger adult patients.[67] In fact, part of the medical evidence suggests that elderly persons have less likelihood of receiving an adequate program of psychotherapy or counseling, compared with younger adult patients.[68] Even studies that have directly compared the prognosis of depression in elderly patients versus younger adults have considered the use of naturalistic methods sufficient and have not used controlled methods for the study of these variables or the different types and levels of treatment that may act as confounding factors. Un to now, only a limited number of studies have recruited elderly and younger patients at the same time and for the same study with a preestablished treatment protocol (that is, an «inception cohort»).[32,33] The evidence from the point of view of the different response to treatment in relationship with age is scarce. One meta-analysis shows us only a very small difference in the response to treatment, and it is unlikely that it has any clinical significance.[69] The results of the naturalistic survey on ECT (which use age at the time of treatment as prediction variable) suggest small or null differences in response to treatment, although the interpretation of these results is difficult, considering their methodological limitations. In comparable studies that have studied both relapses and recurrences, the results seem worse in the elderly age, but the size of these studies and thus the relevance of their conclusions, is rather moderate. Reynolds et al. tried to recruit a cohort of patients with depression in the elderly age and a comparable cohort of patients with depression in younger adult age, although both cohorts were not equally comparable in the clinical aspects. In any event, both groups were distributed randomly for an equivalent treatment, while some laxity was used in regards to the number of depression episodes during the subject's life time. The results indicate that the patients who were already elderly when they entered into the study had a greater likelihood of relapse during the follow-up period. The NIMH Collaborative Depression study also studied patients who were stratified according to entry age into the study and supports the hypothesis that the elderly patients have a shorter interval until recurrence, at least while the possible confounding factors had not been adjusted for.

In regards to studies stratified by age of the first episode, the patients with onset of depression in elderly age have a better response to treatment[34] and lower possibility of subsequent relapse[70] or lower response to the treatment.[71] This discrepancy of results can be understood by the effect of two confounding factors that would act in an opposite or contradictory way.[72] Elderly patients having the same chronological age, but with an early onset age of treatment have a longer disease duration (with more previous episodes) than those with a later onset of the depressive disease. A high number of previous episodes is one of the clearest and strongest prediction factors of relapse and recurrence.[73] However, medical comorbidity is more frequent in depressions of elderly subjects.[39,40] Evidence from

comorbidity studies has shown that time to remission can be longer and remission rates are generally less when comorbidity is present. Thus, inception of depression in the elderly age without medical comorbidity points to a better outcome, but also, at the same time, the inception of depression in the elderly age is associated with a greater medical cormobidity rate. Therefore, a first episode in this group (with medical comorbidity) often entails a worse prognosis.

Thus, the influence of chronological age and inception date of the disease in the prognosis is related with independent type influences, such as previous psychiatric background, current and future comorbidity. As the patient grows older, the presence of comorbid medical diseases has a significant influence, causing a more unfavorable course.[74-76] More important, the influence that depression has on mortality can be observed even after controlling certain factors such as presence of physical disease and other risk factors.[77-79] The subsequent appearance of a dementia picture may be considered as an additional risk associated to the presence of depression in the elderly.[80-82]

In fact, although some comorbid diseases such as high blood pressure or diabetes mellitus are associated with a greater likelihood of receiving adequate care for the depression, this type of relationship is not found in those suffering heart problems or arthritis.[83] Even more, patients who subsequently develop dementia seem to respond worse to the treatment from the beginning.[84] It is of interest to stress that a late onset of depressive disease and greater chronological age seem to predict an increase of the likelihood of having clinical medical comorbidity.[85] The analysis of an extensive study from 1436 centers in phase IV shows that up to an incredible number of 94.1% of depressed patients aged 60 or more presented active medical diseases.[69] The clinical implication of these results is that older patients with medical comorbidity would need longer treatment with antidepressants that would also be well tolerated in the presence of concomitant medical diseases.[86,87]

In summary, the evidence presented by comparative studies seems to indicate that depression in the elderly age responds equally to the initial treatment but follows a more adverse longitudinal pathway than depression in the younger adult age. However, this effect can be explained by factors such as the presence of previous episodes of the depressive disease and also by medical comorbidity. Furthermore, different individuals, and previous response to an antidepressant, and the number of previous episodes may counteract and void the effect of age itself.[88,89] All this requires more verifications, but currently supports the suggesting of applying a longer treatment maintenance period in the elderly age.[90-92] In theory, drug maintenance or cognitive-behavioral therapy could prevent 50% of the disabilities adapted to years of life, if one assumes a 60% treatment adherence.[93]

Unfortunately, only a small proportion of patients are willing to follow a medication plan of more than one year.[94] The prognosis and treatment of depression in the elderly age continues to be of concern, even if we have the evidence that it has improved.[95]

REFERENCES

1. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31:1841.
2. Cole MG, Bellavance F, Mansour A. Prognosis of Depression in Elderly Community and Primary Care Populations: A Systematic Review and Meta-Analysis. Am J Psychiatry 1999; 156:1182-9.
3. Beekman ATF, Geerlings SW, Deeg DJ, Smit JH, Schoevers RS, de Beurs E, et al. The natural history of late-life depression - A 6-year prospective study in the community. Arch Gen Psychiatry 2002;59(7):605-11.
4. Stek ML, Vinkers DJ, Gussekloo J, van der Mast RC, Beekman AT, Westendorp RG. Natural history of depression in the oldest old - Population-based prospective study. Br J Psychiatry 2006;188:65-9.
5. Lewinsohn PM, Clarke G, Seeley JR, Rohde P. Major depression in community adolescents: age at onset, episode duration, and time to recurrence. J Am Acad Child Adolesc Psychiatry 1994;33:809-18.
6. Kendler KS, Walters EE, Kessler RC. The prediction of length of major depressive episode: results from an epidemiological sample of female twins. Psychol Med 1997;27:107-17.
7. Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 2002;181:208-13.
8. Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, et al. Natural history of diagnostic interview schedule/DSM-IV major depression. Arch Gen Psychiatry 1997;54:993-9.
9. McLeod JD, Kessler RC, Landis KR. Speed of recovery from major depressive episodes in a community sample of married men and women. J Abnorm Psychol 1992;101:277-86.
10. Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RM, et al. Time to recovery, chronicity, and levels of psychopathology in major depression - a 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry 1992; 49(10):809-16.
11. Lin EH, Katon WJ, VanKorff M, Russo JE, Simon GE, Bush TM, et al. Relapse of depression in primary care: rate and clinical predictors. Arch Fam Med 1998;7:443-9.
12. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999;156:1000-6.
13. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000;157:229-33.

14. Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. J Clin Psychiatry 2004;65(6):810-9.
15. Spijker J, de Graaf R, Bijl RV, Beekman ATF, Ormel J, Nolen WA. Determinants of persistence of major or depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J Affect Disord 2004;81(3):231-40.
16. Solomon DA, Keller MB, Leon AC, Mueller TI, Shea MT, Warshaw M, et al. Recovery from major depression - A 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997;54(11):1001-6.
17. Gilmer WS, Trivedi MH, Rush AJ, Wisniewski SR, Luther J, Howland RH, et al. Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. Acta Psychiatr Scand 2005;112(6):425-33.
18. Rubenstein LV, Rayburn NR, Keeler EB, Ford DE, Rost KM, Sherbourne CD. Predicting outcomes of primary care patients with major depression: development of a depression prognosis index. Psychiatr Serv 2007;58(8):1049-56.
19. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and Delay in Initial Treatment Contact After First Onset of Mental Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:603-13.
20. Wang PS, Berglund PA, Olfson M, Kessler RC. Delays in initial treatment contact after first onset of a mental disorder. Health Serv Res 2004;39(2):393-415.
21. Mitchell AJ, Subramaniam H. Is Chronological Age or Age of Onset Critical for the Prognosis of Depression? A Systematic Review. Atlanta: American Psychiatric Association Annual Meeting, 2005.
22. Dew MA, Reynolds CF, Houck PR, Hall M, Buysse DJ, Frank E, et al. Temporal profiles of the course of depression during treatment - Predictors of pathways toward recovery in the elderly. Arch Gen Psychiatry 1997;54(11):1016-24.
23. Cattan RA, Barry PP, Mead G, Reefe WE, Gay A, Silverman M. Electroconvulsive-therapy in octogenarians. J Am Geriatr Soc 1990;38(7):753-8.
24. Georgotas A, Mccue RE. The additional benefit of extending an antidepressant trial past 7 weeks in the depressed elderly. Int J Geriatr Psych 1989;4(4):191-5.
25. Ezquiaga E, García A, Pallarés T, Bravo MF. Psychosocial predictors of outcome in major depression: a prospective 12-month study. J Affect Disord 1999;52(1-3):209-16.
26. Perlis RH, Alpert J, Nierenberg AA, Mischoulon D, Yeung A, Rosenbaum JF, et al. Clinical and sociodemographic predictors of response to augmentation, or dose increase among depressed outpatients resistant to fluoxetine 20 mg/day. Acta Psychiatr Scand 2003;108(6):432-8.
27. Grigoriadis S, Kennedy SH, Bagby RM. A comparison of antidepressant response in younger and older women. J Clin Psychopharmacology 2003;23(4):405-7.
28. Riise T, Lund A. Prognostic factors in major depression: A long-term follow-up study of 323 patients. J Affect Disord 2001; 65(3):297-306.
29. Gildengers AG, Houck PR, Mulsant BH, Pollock BG, Mazumdar S, Miller MD, et al. Course and rate of antidepressant response in the very old. J Affect Disord 2002;69:177-84.
30. Mitchell AJ, Subramaniam H. Prognosis of Depression in Old Age Compared to Middle Age: A Systematic Review of Comparative Studies. Am J Psychiatry 2005;162:1588-601.
31. Licht-Strunk E, van der Windt DAWM, van Marwijk HWJ, de Haan M, Beekman AT. The prognosis of depression in older patients in general practice and the community. A systematic review. Fam Pract 2007;24(2):168-80.
32. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, et al. The influence of age on the response of major depression to electroconvulsive therapy - A CORE report. Am J Geriatr Psychiat 2001; 9 (4): 382-390.
33. Katon W, Russo J, Frank E, Barrett J, Williams JW, Oxman T, et al. Predictors of nonresponse to treatment in primary care patients with dysthymia. Gen Hospital Psychiatry 2002; 24(1):20-7.
34. Reynolds CF, Dew MA, Frank E, Begley AE, Miller MD, Cornes C, et al. Effects of age at onset of first lifetime episode of recurrent major depression on treatment response and illness course in elderly patients. Am J Psychiat 1998;155(6):795-9.
35. Reynolds CF, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression. A randomized controlled trial in patients older than 59 years. JAMA 1999;281(1):39-45.
36. Krishnan KRR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, et al. Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry 2002 52(6):559-88.
37. Lenze EJ, Rogers JC, Martire LM, Mulsant BH, Rollman BL, Dew MA, et al. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. Am J Geriatric Psychiatry 2001;9:113-35.
38. Murata T, Kimura H, Omori M, Kado H, Kosaka H, Iidaka T, et al. MRI white matter hyperintensities, H-1-MR spectroscopy and cognitive function in geriatric depression: a comparison of early- and late-onset cases. Int J Geriatr Psychiatry 2001; 16(12):1129-35.
39. Lavretsky H, Lesser IM, Wohl M, Miller BL. Relationship of age, age at onset, and sex to depression in older adults. Am J Geriat Psychiat 1998;6(3):248-56.
40. Tupler LA, Krishnan KRR, McDonald WM, Dombeck CB, D'Souza S, Steffens DC. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. J Psychosomatic Res 2002;53(2):665-76.
41. Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. Psychol Med 1998;28(5):1015-26.
42. Navarro V, Gasto C, Lomena F, Torres X, Mateos JJ, Portella MJ, et al. Prognostic value of frontal functional neuroimaging in late-onset severe major depression. Br J Psychiatry 2004; 184:306-11.
43. Baldwin R, Jeffries S, Jackson A, Sutcliffe C, Thacker N, Scott M, et al. Treatment response in late-onset depression: relationship to neuropsychological, neuroradiological and vascular risk factors. Psychol Med 2004;34(1):125-36.
44. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. Am J Geriatr Psychiatry 1999;7(4):309-16.

45. Baldwin RC, Walker S, Simpson SW, Jackson A, Burns A. The prognostic significance of abnormalities seen on magnetic resonance imaging in late life depression: Clinical outcome, mortality and progression to dementia at three years. Int J Geriatr Psychiatry 2000;15(12):1097-104.
46. Heiden A, Kettenbach J, Fischer P, Schein B, Ba-Ssalamah A, Frey R, et al. White matter hyperintensities and chronicity of depression. J Psychiatr Res 2005;39(3):285-93.
47. Iosifescu DV, Nierenberg AA, Alpert JE, Smith M, Bitran S, Dording C, et al. The impact of medical comorbidity on acute treatment in major depressive disorder. Am J Psychiatry 2003;160(12):2122-7.
48. Small GW, Birkett M, Meyers BS, Koran LM, Bystritsky A, Nemeroff CB. Impact of physical illness on quality of life and antidepressant response in geriatric major depression J Am Geriatr Society 1996;44(10):1220-5.
49. Perlis RH, Iosifescu DV, Alpert J, Nierenberg AA, Rosenbaum JF, Fava M. Effect of medical comorbidity on response to fluoxetine augmentation or dose increase in outpatients with treatment-resistant depression. Psychosomatics 2004;45(3): 224-9.
50. Sheikh JI, Cassidy EL, Doraiswamy PM, Salomon RM, Hornig M, Holland PJ, et al. Efficacy, safety, and tolerability of sertraline in patients with late-life depression and comorbid medical illness. J Am Geriatr Society 2004;52(1):86-92.
51. Bogner HR, Cary MS, Bruce ML, Reynolds CF, Mulsant B, Ten-Have T, et al. The role of medical comorbidity in outcome of major depression in primary care: The PROSPECT study. Am J Geriatr Psychiatry 2005;13(10):861-8.
52. Cole MG, Bellavance F. Depression in elderly medical inpatients: a meta-analysis of outcomes. CMAJ 1997;157:1055-60.
53. Oslin DW, Datton CJ, Kallan MJ, Katz IR, Edell WS, Ten-Have T. Association between medical comorbidity and treatment outcomes in late-life depression. J Am Geriatr Society 2002; 50:823-8.
54. Bogner HR, Bruce ML, Reynolds CF, Mulsant BH, Cary MS, Morales K, et al. The effects of memory, attention, and executive dysfunction on outcomes of depression in a primary care intervention trial: the PROSPECT study. Int J Geriatr Psychiatry 2007;22(9):922-9.
55. National Institute of Health Consensus panel. NIH consensus development panel on depression in late life, diagnosis and treatment of depression in late life. JAMA 1992;268:1018-24.
56. Wagner HR, Burns BJ, Broadhead WE, Yarnall KSH, Sigmon A, Gaynes BN. Minor depression in family practice: functional morbidity, co-morbidity, service utilization and outcomes. Psychol Med 2000;30(6):1377-90.
57. Hermens MLM, van Hout HPJ, Terluin B, van der Windt DA, Beekman AT, van Dyck R, et al. The prognosis of minor depression in the general population: a systematic review. General Hospital Psychiatry 2004;26(6): 453-62.
58. Vuorilehto M, Melartin T, Isometsa E. Depressive disorders in primary care: recurrent, chronic, and co-morbid. Psychol Med 2005;35(5):673-82.
59. Judd LL. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 1997;54:989-91.
60. Brodaty H, Luscombe G, Peisah C, Anstey K, Andrews G. A 25 year longitudinal, comparison study of the outcome of depression. Psychol Med 2001;31:1347-59.
61. Thornicroft G, Sartorius N. The course and outcome of depression in different cultures: 10-year follow-up of the WHO Collaborative Study on the Assessment of Depressive Disorders. Psychol Med 1993;23:1023-32.
62. Angst J, Preisig M. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995; 146(1):5-16.
63. Kennedy N, Foy K, Sherazi R. McDonough M. McKeon P. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disord 2007;9(1-2):25-37.
64. Katon WJ, Unutzer A, Simon G. Treatment of depression in primary care. Where we are, where we can go. Med Care 2004; 42(12):1153-7.
65. Tai-Seale M, Bramson R, Drukker D, Hurwicz ML, Ory M, Tai-Seale T, et al. Understanding primary care physicians' propensity to assess elderly patients for depression using interaction and survey data. Med Care 2005;43(12):1217-24.
66. Pfaff JJ, Almeida OP. A cross-sectional analysis of factors that influence the detection of depression in older primary care patients. Aust N Z J Psychiatry 2005;39(4):262-5.
67. Stoppe G, Sehmer-Kurz K. Patients' and physicians' therapy expectations and treatment outcome of hospital treated depression - a comparison of younger and older patients. Eur Psychiatry 2004;19(1):212S-213S.
68. Stoppe G, Sehmer-Kurz K. Patients' and physicians' therapy expectations and treatment outcome of hospital treated depression - a comparison of younger and older patients. Eur Psychiatry 2004;19(1):S212-S13.
69. Rush AJ, Rothschild T. Efficacy and safety profile of escitalopram in the elderly: findings from a naturalistic clinical study of major depressive disorder. Poster at the 17th Annual Meeting of the American Association for Geriatric Psychiatric Feb 221-24, Baltimore.
70. Brodaty H, Harris L, Peters K, Wilhelm K, Hickie I, Boyce P, et al. Prognosis of depression in the elderly: a comparison with younger patients. Br J Psychiatry 1993;163,589-96.
71. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Feder M, Einhorn A, et al. Recovery in geriatric depression Arch Gen Psychiatry 1996;53(4):305-12.
72. Subramaniam H, Mitchell AJ. The prognosis of depression in late life versus mid-life: implications for the treatment of older adults. Int Psychogeriatr 2005;17(4):533-8.
73. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression - Remission and beyond. JAMA 2003;289(23):3152-60.
74. Schulz R, Drayer RA, Rollman BL. Depression as a Risk Factor for Non-Suicide Mortality in the Elderly. Biol Psychiatry 2002; 52:205-25.
75. Reynolds CF, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, et al. Maintenance treatment of major depression in old age. N Engl J Med 2006;354(11):1130-8.
76. Baune BT, Adrian I, Jacobi F. Medical disorders affect health outcome and general functioning depending on comorbid major depression in the general population. J Psychosom Res 2007;62(2):109-18.
77. Everson-Rose SA, House JS, Mero RP. Depressive symptoms and mortality risk in a national sample: Confounding effects of health status. Psychosom Med 2004;66(6):823-30.

78. Murphy JM, Burke JD, Monson RR, Horton NJ, Laird NM, Lesage A, et al. Mortality associated with depression - A forty-year perspective from the Stirling county study. Soc Psychiatry Psychiatr Epidemiol 2008;43(8):594-601.
79. Rapp MA, Gerstorf D, Helmchen H, Smith J. Depression predicts mortality in the young old, but not in the oldest old: Results from the Berlin Aging study. Am J Geriatr Psychiatry 2008; 16(10):844-52.
80. Mitchell AJ. Is depression a risk factor for subsequent dementia: A systematic review and meta-analysis of 39 cohort studies. Neurology 2006;66(5):A348-A348.
81. Mitchell AJ. Depression as a risk factor for later dementia: a robust relationship? Age Ageing 2005;34(3):207-9.
82. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. Gerontology 2000;46(4):219-27.
83. Harman JS, Edlund MJ, Fortney JC, Kallas H. The influence of comorbid chronic medical conditions on the adequacy of depression care for older Americans. J Am Geriatr Soc 2005; 53(12):2178-83.
84. Brodaty H, Hickie I, Mason C, Prenter L. A prospective follow-up study of ECT outcome in older depressed patients. J Affect Disord 2000;60(2):101-11.
85. Philibert RA, Richards L, Lynch CF, Winokur G. The effect of gender and age at onset of depression on mortality. J Clin Psychiatry 1997;58(8):355-60.
86. Gill D, Hatcher S. A systematic review of the treatment of depression with antidepressant drugs in patients who also have a physical illness. J Psychosom Res 1999;47(2):131-43.
87. Enns MW, Swenson JR, McIntyre RS, Swinson RP, Kennedy SH. Clinical guidelines for the treatment of depressive disorders VII. Comorbidity. Can J Psychiatry 2001;46(Supl.):77-90.
88. Tew JD, Mulsant BH, Houck PR, Lenze EJ, Whyte EM, Miller MD, et al. Impact of prior treatment exposure on response to antidepressant treatment in late life. Am J Geriatr Psychiatry 2006; 14(11):957-65.
89. Driscoll HC, Basinski J, Mulsant BH, Butters MA, Dew MA, Houck PR, et al. Late-onset major depression: clinical and treatment-response variability. Int J Geriatr Psychiatry 2005;20(7):661-7.
90. Baldwin RC, Anderson D, Black S, Evans S, Jones R, Wilson K, et al. Guideline for the management of late-life depression in primary care. Int J Geriatr Psychiatry 2003;18(9):829-38.
91. Jacoby R. How long should the elderly take antidepressants? A double blind placebo controlled study of continuation/prophylaxis therapy and dothiepin. BMJ 1993;162:175-82.
92. Segal ZV, Pearson JL, Thase ME. Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. J Affect Disord 2003; 77(2):97-108.
93. Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. Arch Gen Psychiatry 2004; 61(11):1097-103.
94. Mullins CD, Shaya FT, Meng FL, Wang JL, Harrison D. Persistence, switching, and discontinuation rates among patients receiving sertraline, paroxetine, and Citalopram. Pharmacotherapy 2005;25(5):660-7.
95. Montagnier D, Barberger-Gateau P, Jacqmin-Gadda H, Dartigues JF, Rainfray M, Pérès K, et al. Evolution of prevalence of depressive symptoms and antidepressant use between 1988 and 1999 in a large sample of older French people: Results from the Personnes Agees Quid Study. J Am Geriatr Society 2006; 54(12):1839-45.