Clinical research

Long-term course and outcome of depression in later life

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Depression in later life is usually a recurrent illness and often a chronic one, associated with increased health care utilization, amplification of the disability born of concurrent medical illness, decreased quality of life, increased risk for suicide, and cognitive impairment. The good news, however, is that maintenance treatments work and have a demonstrably positive impact on long-term illness course. Treatment response is especially variable, or brittle, in patients aged over 70; yet maintenance treatment with combined medication and psychotherapy is able to significantly reduce long-term treatment response variability, ensuring continued wellness. Further evaluation of cost-effectiveness is necessary in order to improve reimbursement for effective long-term treatment.

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Getting well is not enough; it is staying well that counts. This theme has guided our research and clinical practice over the past decade, in completing the first long-term controlled studies of maintenance pharmacotherapy and psychotherapy ever conducted in geriatric depression.[1] Recent data from the World Health Organization (WHO),[2] clearly illustrate the importance of taking a long-term view of the clinical management of depression in later life (and, indeed, across the life cycle). According to the WHO, unipolar major depression and suicide accounted for 5.1% of the global burden of disease in 1990, as measured in disability-adjusted life years. Of relevance to intervention research in geriatric depression, the significance of illness burden attributable to depression increases with age weighting and thus will grow further by the year 2020 based upon projected demographic shifts towards an older population. Hence, finding ways of preventing the return of depression in elderly patients and of maintaining the gains of acute and continuation treatment would represent a significant treatment advance and contribution to public health.

Data from naturalistic studies (not controlling for treatment or treatment intensity) have identified several correlates of relapse and recurrence in geriatric depression. Correlates, or predictors, of a relapsing course include a history of frequent prior episodes, dysthymia, a first onset of major depression after the age of 60, supervening medical illness, high pretreatment severity of depression and anxiety, incomplete recovery, and cognitive impairment, especially frontal lobe dysfunction as signaled by difficulties in initiation or perseveration.[3-10] Our own studies have suggested that patients aged 70 and older show more variable, or brittle, long-term treatment response, probably reflecting the complex biological and psychosocial substrates of geriatric depression.[11] It is also patients over age 70 who represent a rapidly increasing segment of the elderly population, whose response to antidepressant treatment may be the least predictable, and in whom

depression will increasingly represent a source of excess medical service utilization and economic cost, and reduced quality of life, morbidity, and mortality during the next 20 years.[2,12]

Despite the evidence that high treatment intensity is effective in preventing relapse and recurrence,[9] the intensity of antidepressant treatment prescribed by psychiatrists begins to decline within 16 weeks of entry and approximately 10 weeks prior to full recovery.[4] Residual symptoms of anxiety and excessive worrying predict early recurrence after tapering continuation treatment in elderly depressed patients.[10] Naturalistic studies, while important for understanding the illness course of geriatric depression, leave unanswered questions of importance to patients, caregivers, clinicians, and health policy analysts: Can long-term antidepressant treatment (whether pharmacological, psychosocial, or a combination of both) affect the course of depression in the elderly, especially those over age 70 in whom treatment response is more variable and unpredictable? If so, what types of treatment are effective in which patients, ie, how can clinicians better match patients and treatment to serve the long-term benefit of the patient? We have addressed these questions in the research described below.

The first Pittsburgh study of maintenance therapies in late-life depression (MTLD-1)

Goal and hypotheses of the MTLD-1 study

In order to address the need for controlled data on the long-term clinical management of geriatric depression, we undertook in 1989, with the support of the National Institute of Mental Health, the first long-term studies of maintenance pharmacotherapy and psychotherapy ever conducted in recurrent major depressive illness of later life. We tested the hypothesis that maintenance pharmacotherapy with nortriptyline (NT) and monthly maintenance interpersonal psychotherapy (IPT), either singly or in combination, are superior to placebo in preventing or delaying recurrence of major depressive episodes in the elderly; and that combined treatment with both antidepressant medication and interpersonal psychotherapy is superior to either alone in main-

taining recovery and preventing return of depressive illness.

Summary of methods

The MTLD-1 study recruited 187 elderly patients aged 60 and over with recurrent, nonpsychotic, nondysthymic, unipolar major depression. Two thirds of the study group were aged 60 to 69, and one third were 70 and older. Three quarters of the sample were women and 93% were white. On average, patients were in their fourth lifetime episode of major depression at study entry and had moderate-to-severe depressive symptoms. About 15% had a history of suicide attempts, and about 16% required inpatient treatment during their index episode. Most patients had 5 to 6 chronic medical problems, in addition to depression, for which they were receiving treatment. This sample had no-to-minimal cognitive impairment, as measured by the Folstein Mini-Mental State.[13] About half of the study group were recruited through clinical referral, and half in response to media announcements and presentations to lay groups in the community.

After providing written informed consent, patients received open combination treatment with NT and weekly IPT.[14] We titrated NT doses to achieve steady-state levels of 80 to 120 ng/mL. The goal of acute-phase combined treatment was to achieve remission of depressive symptoms. The median time to remission was 12 weeks, but speed of response was highly variable.[15]

Following successful acute treatment, patients began a 16-week period of continuation therapy, to ensure stability of remission and to ensure full recovery. Continuation treatment consisted of combined NT and IPT, using the same dose of NT (an average of 85 mg/day, but with a range of 20 to 200 mg/day) as during acute therapy, but reducing the frequency of IPT to twice monthly.

Patients with stable remission and recovery entered the experimental maintenance phase of the study, via double-blind random assignment to one of four long-term treatment conditions: (i) medication clinic with NT; (ii) medication clinic with placebo; (iii) monthly maintenance IPT with NT; and (iv) monthly maintenance IPT with placebo. Patients remained in maintenance therapy for 3 years, or until recurrence of major depression, whichever occurred first. Survival analysis tested differences in rates of recurrence and time to recurrence.

Outcomes of therapy at each phase of treatment: acute, continuation, and maintenance

Acute treatment

Of 187 patients who signed informed consent to participate, 5 showed spontaneous remission and 2 declined to begin treatment. Thus, 180 patients actually began acute treatment with NT and IPT, and of these 159 completed acute-phase treatment (140 remitters and 19 nonresponders). Twenty-one patients dropped out of acute-phase treatment, 8 refusing further treatment, 6 developing medical conditions contraindicating NT, 2 being noncompliant, and 1 each dying or becoming delusional or manic.

The median time to remission in this sample was 12 weeks,[16] and the earliest point of statistically reliable discrimination of recovering and nonrecovering patients was 4 weeks.[17] Almost one third (30.5%) showed rapid sustained response to combined treatment with NT and IPT, ie, they were well by 4 weeks. Other patients remitted more slowly, by 8 to 10 weeks (22.1%), while the remaining patients showed partial or mixed response. Slower and more variable treatment response was associated with higher pretreatment levels of anxiety, lower levels of social support, greater current age at study entry, and higher percentage of rapid eye movement (REM) sleep before the initiation of treatment.[15] Subjects with earlier-onset depressive illness (ie, first episode prior to age 60) took on average 5 to 6 weeks longer to achieve remission, possibly a reflection of the greater number of prior lifetime episodes (chronicity).[18] Because early-onset subjects also had a higher rate of past suicide attempts, we concluded that they need especially careful surveillance during acute treatment, since they are likely to take longer to respond.

Continuation treatment

Of the 140 remitters who entered continuation treatment, 124 met study criteria for recovery at the end of 16 weeks of continuation treatment. Nine patients relapsed and could not be restabilized. Seven subjects dropped out of treatment, either noncompliant or refusing further treatment altogether. Thus, 124 patients were randomly assigned to a long-term maintenance therapy condition. During the 6-week period of double-blind transition to maintenance therapy, when NT was gradually tapered and placebo substituted, 13 subjects suffered relapse. A total of 107 fully recovered patients actually began maintenance treatment. Overall, we observed that the rate of treatment resistance to combined treatment with NT and IPT, as determined by failure to remit or by subsequent relapse during continuation treatment and failure to recover, was 18%.[19]

Maintenance treatment

The primary outcome measure of the MTLD-1 study was recurrence of major depressive episodes, versus continued wellness. Both NT (steady-state levels of 80 to 120 ng/mL) and monthly maintenance IPT worked better than placebo/medication clinic in preventing recurrences of major depression. The best 3-year outcome was observed with combined NT and IPT.[1] Of patients randomly assigned to combined treatment, only 20% suffered recurrence during the 3 years of maintenance treatment, whereas 90% of those on placebo suffered recurrence of their depression. Recurrence rates were intermediate for those in monotherapy: 43% for maintenance NT and 64% for monthly maintenance IPT with placebo.

Higher age at study entry was associated with a greater liability to recurrence, manifest by higher recurrence rates generally in those 70 and older. A similar percentage of subjects aged 70 and above (40/67, or 59.7%) entered maintenance treatment, as among subjects aged 60 to 69 (70/113, or 61.9%). Nonetheless, despite identical recovery rates during acute and continuation therapy with combined treatment, the overall recurrence rate during the first year of maintenance treatment was 60.5% (23/40) in subjects aged 70 and older, versus 30.4% (21/69) in those aged 60 to 69.[11]

The steady-state blood level targeted and achieved in the MTLD-1 study was 80 to 120 ng/mL, with daily doses ranging from 20 to 200 mg. Doses and blood levels established in the initial acute phase of therapy were continued into maintenance therapy. In order to test further whether the effective prophylactic dose is the same as the acute-phase dose, we conducted a second parallel study comparing two fixed, steady-state levels of NT: 80 to 120 ng/mL versus 40 to 60 ng/mL. Recurrence rates did not in fact differ significantly in the two maintenance conditions: 40% recurrence over 3 years in the 80 to 120 ng/mL condition versus 29% recurrence in

Clinical research

the 40 to 60 ng/mL condition. Residual depressive symptoms and minor depressive episodes were more frequent among patients in the 40 to 60 ng/mL condition, however, while complaints of constipation were more frequent and persistent in the 80 to 120 ng/mL condition.[20] Full-dose maintenance treatment with NT appears to be preferable to lower-dose maintenance because of fewer residual symptoms and less variability of treatment response, as long as the side-effect burden can be managed effectively.

In addition to addressing our primary question (ie, does maintenance treatment make a difference in long-term illness course?), we also addressed the issue of matching patient with treatment. We reported that monthly maintenance IPT, without medication, was effective in preventing recurrence in patients who reported normal subjective sleep quality by early continuation treatment.[21] We also observed that long-term response to maintenance IPT alone was correctly predicted in 80% of cases by the level of pretreatment depressive symptoms. Patients with lesser severity of depression, as manifested by pretreatment Hamilton depression scores of under 20, generally did well with maintenance IPT alone, whereas those with more severe depressions, as manifested by score of 20 or greater, did better on NT.[22]

Conclusion

The good news is that long-term antidepressant treatment can indeed affect the course of depressive illness positively in later life, helping to maintain wellness and engagement in life. Combined treatment using both antidepressant medication and monthly interpersonal psychotherapy was associated with the highest 3-year continued-recovery rates (80% in all patients and 67% in those aged 70 and above). The success of combined treatment in the elderly attests to the interplay of biological and psychosocial factors in the onset and offset of geriatric depression. The greater medical burden of elderly patients, the frequency of bereavement and role-transition issues, and the tendency of impaired sleep quality to persist even into remission, all suggest why a combined treatment approach may be helpful in dealing with the liability to recurrence posed by the frail health and depletion of psychosocial resources characteristic of the elderly with depression.

Where does the field need to go from here? In the decade since we undertook the MTLD-1 study, newer antidepressant medications, the selective serotonin reuptake inhibitors (SSRIs), have become available, which are better tolerated by the elderly, safer in the context of concurrent medical illnesses than tricyclics, and much less likely to be fatal in overdose. Thus, testing the maintenance efficacy of SSRIs, especially in patients aged 70 and above, has the potential of substantial generalizability. However, due to the lack of controlled data from geriatric maintenance trials evaluating SSRIs, clinicians must extrapolate from studies of midlife patients.[23,24] Because combined treatment with medication and IPT may be the optimal clinical strategy for prevention of recurrence, we believe that controlled evaluation of SSRI antidepressant pharmacotherapy combined with interpersonal psychotherapy should now be undertaken in over-70 subjects.

Even if the science bears good news about our ability to positively affect the long-term illness course of geriatric depression through the use of combined therapy, the bad news is that current reimbursement for mental health care in later life falls far short of the mark. There have been no studies of the cost-effectiveness (that is, ratio of dollar costs of a treatment to quality adjusted life years gained by the treatment) for depression interventions in the elderly. Given the science of our field, the issue, we believe, is not whether a given treatment is more cost-effective than no treatment, but specifically whether combined medication and psychotherapy is more cost-effective than medication monotherapy. Clearly this issue has public health policy implications as well as implications for clinicians as they decide which treatment is most appropriate for their elderly patients. The Pittsburgh MTLD-2 study aims to achieve the objective set forth here of evaluating the long-term efficacy of SSRI therapy, with and without IPT, together with an assessment of the relative cost-effectiveness of combined treatment versus medication alone. ❏

REFERENCES

1. Reynolds, CF, Frank E, Perel JM, Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA.* 1999;28:39-45.
2. World Health Organization. Global Health Statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. In: *The Global Burden of Disease.* Cambridge, Mass: Harvard University Press; 1996.
3. Zis AP, Grof P, Webster M. Predictors of relapse in recurrent affective disorders. *Psychopharmacol Bull.* 19801;6:47-49.
4. Alexopoulos GS, Meyers BS, Young RC, et al. Recovery in geriatric depression. *Arch Gen Psychiatry.* 1996;53:305-312.
5. Cole MG, Bellavance F. The prognosis of depression in old age. *Am J Geriatr Psychiatry.* 1997;5:4-14.
6. Baldwin RC, Jolley DJ. The prognosis of depression in old age. *Br J Psychiatry.* 1986;149:574-583.
7. Burvill PW, Hall WD, Stampfer HG. The prognosis of depression in old age. *Br J Psychiatry.* 1991;158:64-71.
8. Keller MB, Lavori PW, Collins CE, Klerman GL. Predictors of relapse in major depressive disorder. *JAMA.* 1983;250:3299-3304.
9. Georgotas A, McCue RE. Relapse of depressed patients after effective continuation therapy. *J Affect Disord.* 1989;17:159-164.
10. Meyers BS, Gabriele MS, Kakuma T, Ippolito L, Alexopoulos G. Anxiety and recurrence as predictors of recurrence in geriatric depression: a preliminary report. *Am J Geriatr Psychiatry.* 1996;4:252-257.
11. Reynolds CF, Frank E, Dew MA, et al. Treatment of 70+ year olds with recurrent major depression. Excellent short-term but brittle long-term response. *Am J Geriatr Psychiatry.* 1999;7:64-69.
12. Unutzer J, Patrick DL, Simon G. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. *JAMA.* 1997;277:1618-1623.
13. Folstein MF, Folstein SW, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.
14. Klerman GL, Weissman MM, Rounsaville BJ, Chevron E. *Interpersonal Psychotherapy of Depression.* New York, NY: Academic Press, Basic Books Inc; 1984.
15. Dew MA, Reynolds CF, Houck PR, et al. Temporal profiles of the course of depression during treatment: predictors of pathways toward recovery in the elderly. *Arch Gen Psychiatry.* 1997;54:1016-1024.
16. Reynolds CF, Frank E, Perel JM, et al. Treatment of consecutive episodes of major depression in the elderly. *Am J Psychiatry.* 1994;151:1740-1743.
17. Reynolds CF, Frank E, Dew MA, et al. Discrimination of recovery in the treatment of elderly patients with recurrent major depression: limits of prediction. *Depression.* 1995;2:218-222.
18. Reynolds CF, Dew MA, Frank E, 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 Psychiatry.* 1998;155:795-799.
19. Little JT, Reynolds CF, Dew MA, et al. How common is resistance to treatment in recurrent, nonpsychotic geriatric depression? *Am J Psychiatry.* 1998;155:1035-1038.
20. Reynolds CF, Perel JM, Frank E, et al. Three-year outcomes of maintenance nortriptyline in late-life depression: a study of two fixed, plasma levels. *Am J Psychiatry.* 1999;156:1177-1181.
21. Reynolds CF, Frank E, Houck, PR, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry.* 1997;154: 958-962.
22. Taylor MP, Reynolds CF, Frank E. Which elderly depressed patients remain well on maintenance interpersonal psychotherapy alone? A report from the Pittsburgh study of maintenance therapies in late-life. *Depress Anxiety.* In press.
23. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. *Int Clin Psychopharmacol.* 1993;8:189-195.
24. Montgomery SA, Rasmussen JGC, Tanghoj P. A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *Int Clin Psychopharmacol.* 1993;8:181-188.

Evolucion a largo plazo y consecuencias de la depresion de aparicion tardia

La depresión en los estadios avanzados de la vida es generalmente una enfermedad recurrente y a menudo crónica, que se acompa_a de una utilización creciente de atención médica, de una amplificación de las incapacidades causadas por enfermedades somáticas concurrentes, de un menoscabo de la calidad de vida, de un aumento desl riesgo de suicidio y de deterioro cognoscitivo. Sin embargo, hay novedades alentadoras que señalan que los tratamientos de mantención resultan eficaces y poseen un impacto positivo demostrable sobre la evolución a largo plazo de la enfermedad. La respuesta al tratamiento es especialmente variable o inconsistente en pacientes de más de 70 años; por consiguiente, asociar en el tratamiento de mantención medicación y psicoterapia puede reducir significativamente la variabilidad de la respuesta al tratamiento en el largo plazo y garantizar beneficios continuos. Es necesaria una evaluación adicional respecto a la relación costo-efecto con el fin de mejorar la adherencia a un tratamiento duradero eficaz.

La dépression du sujet âgé : évolution et pronostic à long terme

La dépression du sujet âgé est habituellement une maladie récidivante, mais aussi volontiers chronique. Elle s'associe à un recours accru au système de santé, à une amplification du handicap du fait de pathologies associées, à une baisse de la qualité de vie, à une augmentation du risque suicidaire et à des perturbations des fonctions cognitives. En contrepartie, il faut souligner l'efficacité du traitement d'entretien qui exerce même un impact positif démontré sur l'évolution de la maladie à long terme. La réponse au traitement est particulièrement variable, ou fragile, notamment chez les sujets âgés de plus de 70 ans. Cependant, le traitement d'entretien, dès lors qu'il associe les médicaments et la psychothérapie, est capable de réduire significativement les fluctuations de la réponse thérapeutique à long terme et d'assurer la continuité du bien-être. Des études coût-efficacité complémentaires sont néanmoins nécessaires pour améliorer le remboursement des traitements qui font la preuve de leur efficacité au long cours.