The concept of depression as a disease goes back a long way. Hippocrates described melancholia as a condition in which patients had fears and despondencies for a long time. Robert Burton’s book, *Anatomy of Melancholy*, from 1621, is a most interesting read, and many of the descriptions are still applicable. In the last 200 years many concepts have been introduced into the classification of depression, including manic-depressive disorder/insanity, bipolar disorder, and depression. Kraepelin’s original concept of manic-depressive disorder has evolved into the concept of polarity, and bipolar and unipolar disorders. Psychiatric classification is characterized by an inflation of the diagnostic categories, including subtypes of depression. This rapid multiplier effect is primarily descriptive, and there is a need to rethink, in a pragmatic fashion, the classification system, in order to develop one that is likely to be of utility and which has a scientific basis. Is the time now right to ask whether there are essential conditions relevant to depression? I think that it is, and here I will introduce the notion with two such conditions. The first is early life stress disorder, and the second vascular depression. These conditions have reached a point where the data supports them as distinct entities. In this paper, the rationale for this is discussed.

**Keywords:** depression; classification; taxonomy; vascular; early life stress disorder

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Defining psychiatric disease in a nominalist tradition

There are two methods of labeling disease. Nominalist and essentialist. Nominalists label symptoms with a disease name, and etiology is not a factor. The current approach to depression follows the symptom- and course-based identification of syndromes/diseases. In this tradition, the names of diseases are an easy way of briefly stating the status of symptoms and signs as well as course. The causes in this type of classification can be elusive. Say, for instance, we find that patients with disease X, eg, major depression, have an abnormal genetic marker. We can use the data and develop them as a test to identify specificity, sensitivity, etc. However, this approach relates the changes only to that initial definition. If the definition was not accurate in the first place, then it becomes a problem. It can lead to a test for that condition, but it does not change the definition of that condition based on a presumed cause. Now let us say that the test is a mutation in a gene, and that mutation links not just to depression but to anxiety disorder, bipolar disorder, attention deficit disorder, etc then a symptom-based approach will be disadvantageous. It is likely not to change our understanding, and may be an impediment to better identification of subjects and treatments. An example of an essentialist identification is Hepatitis B or C. Here, there is no link to symptoms or signs—just to the cause. The doctor’s skill then consists in identifying the causal disease and prescribing the appropriate treatment. This concept of disease is not yet applicable in a broad sense to psychiatry, because much less is known, and causation is likely to be multifactorial. However, as evidence of causation develops, an essentialist mentality can move the field forward.

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) points out that “there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder” (p 21), but the mere fact that a diagnostic concept is listed, official, and provided with a precise definition makes it appear robust and specific. Definitions are stated to become codified and reified without an examination of the fundamental validity. Robins and Guze proposed formal criteria for establishing the validity of psychiatric diagnoses; however few of the entities in DSM meet these criteria. As Kendell and others have pointed out, it is likely that the concept of a nominalist description of disease in the psychiatric context as a distinct entity may not be relevant. One of the hallmarks for symptom- and course-based identification is to demonstrate points of nonoverlap between similar syndromes. The points of rarity between psychiatric diseases defined in a nominalist tradition are not as distinct
as one would like. On the other hand, an essentialist clas-
sification may be very relevant. We have recently noted
a system for defining a condition as a disease.

Criteria for defining disease

The first and obvious criterion is that the condition
should be one that leads to a risk for adverse outcomes—
either mortality or functional impairment.\textsuperscript{12}
The second is where an identifiable characteristic genetic
or environmental factor or pathology can be clearly
defined. This characteristic should separate the entity
from similar entities, in terms of at least one of the fol-
lowing criteria:

1. Clinical symptoms
2. Course and outcome
3. Familial pattern
4. Treatment response.

The differentiation should be clinically significant.
Clinical significance may have to be adjudicated by col-
lective groups. The failure to separate may change over
time as additional information is developed, and may go
through a stage where the characteristic is considered as
a subentity.\textsuperscript{12,13}

Is the time right to ask whether there are potential essen-
tialist conditions relevant to depression? I think it is, and
I would like to introduce the notion of two such cate-
gories. The first is early life stress disorder, and the sec-
ond vascular depression; both these entities have reached
a point where the data appears to support their consid-
eration as distinct entities that are clinically significant.

Early life stress disorder

Early life stress disorder meets the essential require-
ments for what should be called a specific entity. The past
decade has seen an increasing awareness of the presence
and high incidence of child maltreatment.\textsuperscript{14} The National
Center of Child Abuse and Neglect reports approxi-
mately 1.5 million cases of child maltreatment annually
in the United States; half of these cases represent neglect,
and 700 000 cases are of sexual, physical, or emotional
abuse. In addition to child maltreatment, children often
experience other losses, such as the loss of a parent.\textsuperscript{15}
Thus, early childhood stress is quite common. In a ran-
don sample of 1442 subjects from the United States,
14.2\% of men and 32.3\%, of women reported childhood
sexual abuse, and 22.2\% of males and 19.5\%, of females
reported physical abuse.\textsuperscript{14} Childhood sexual and physical
abuse is common in the general population. So what do
we know about the effect of childhood stress?
There is overwhelming evidence that early life stress con-
tinues a major risk factor for depression. Increased rates
of major depression, post-traumatic stress disorder
(PTSD), attention-deficit/hyperactivity disorder, and
other behavioral disorders have been reported for mal-
treated children (eg, refs 17,18). A community-based
study of adult women revealed that those with a history
of childhood sexual or physical abuse had more symp-
toms of depression and anxiety and more frequently
attempted suicide than women without a history of child-
hood abuse.\textsuperscript{19} Others have reported that major depres-
sion and anxiety disorders, including panic disorder and
PTSD, are frequent in adults with a history of childhood
abuse (eg, refs 20,21). Similar findings have been
reported for other instances of early life stress. For exam-
ple, early parental loss has been found to be related to
unipolar and bipolar depression, as well as anxiety dis-
orders, beyond familial or genetic factors.\textsuperscript{22}

One could argue therefore that early adverse experiences
may “shape” a preexisting genetic vulnerability to stress
and disease, resulting in a stable phenotype, with a cer-
tain risk of developing one syndrome or another in
response to further stress exposure. One can argue that
this constitutes the essential component of disease, ie, it
is state that places an individual at an increased risk for
adverse consequences.

This state can be defined as distinct from the rest of
the population, and in addition can be differentiated on
the following bases.

Clinical

By definition these individuals can exhibit a plethora of
symptoms ranging from anxiety, violent behavior, depres-
sion, personality disorder, drug abuse, etc. As noted
above, an overview of the literature shows that individu-
als who suffer abuse or neglect as children are more
likely to be depressed, to experience other types of psy-
chiatric illness, to have more physical symptoms, and to
engage in drug and alcohol abuse. Clearly, additional
work is needed to differentiate features. In fact when one
works with these patients it is interesting to note the flux
in symptom course and features over time. In real life,
few of these patients are likely to be true to any one cur-
rent diagnostic (DSM) entity.
Course and outcome

Childhood abuse strongly predicts poor psychiatric and physical health outcomes in adulthood. Individuals with a history of childhood abuse, particularly sexual abuse, are more likely than individuals with no history of abuse to become high utilizers of medical care and emergency services.

Biological

Findings in children

Neuroendocrine dysfunction in children with early life stress is highly variable, and likely influenced by multiple factors. This could be because a stable phenotype of altered stress vulnerability may not yet have developed in children. Some studies report decreased salivary cortisol concentrations in the morning or a lack of decline of cortisol toward the evening, evidence of an altered circadian rhythm of the hypothalamo-pituitary-adrenal (HPA) axis.23-25 Cortisol concentrations are related to symptoms of depression. Serotonergic dysfunction is also seen in abused children.26 In contrast to findings in adult depression and PTSD, normal hippocampal volumes have been observed in maltreated children with PTSD,27 although smaller ratios of N-acetylasparate to creatine have been found in the anterior cingulate of abused children with PTSD.28

Findings in adults

A limited number of retrospective studies have evaluated the long-term consequences of early life stress in adults. Lemieux and Coe39 observed increased 24-hour urinary cortisol excretion in women with a history of childhood sexual abuse and PTSD. These findings, interestingly, are opposite to findings in Vietnam veterans and Holocaust survivors with PTSD.30 Increased plasma cortisol concentrations are seen amongst patients who experienced the death of a parent in childhood.31 On the other hand, women with a history of childhood sexual abuse were found to show hypersuppression of salivary cortisol concentrations in response to a low dose of dexamethasone.32 These data, even if they are variable, are consistent with the notion that childhood abuse leaves a scar in the stress response axis. Heim et al found that abused women exhibit markedly increased plasma acetylcholine (ACTH) responses to psychosocial laboratory stress and in response to corticotrophin-releasing factor (CRF) compared with control subjects and depressed women without early life stress.33 Similar changes are seen in the sympathetic response.29,34 These findings are consistent with findings from animal studies, suggesting that the stress axis is sensitized after early life stress in humans that could be due to an increased risk for psychopathology. Decreased hippocampal volumes have been measured in adults with perinatal trauma and adult women with child abuse and PTSD.35 It is unclear whether this is secondary to the trauma or pre-existent.

Treatment

Obviously the treatment of this entity has to be directed towards prevention. However, it also has implications for medication treatment. In one study, 681 patients with chronic forms of major depression were treated with an antidepressant (nefazodone), Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or the combination. Overall, the effects of the antidepressant alone and psychotherapy alone were equal, and significantly less effective than combination treatment. However, among those with a history of early childhood trauma (loss of parents at an early age, physical or sexual abuse, or neglect), psychotherapy alone was superior to antidepressant monotherapy.36 Moreover, the combination of psychotherapy and pharmacotherapy was only marginally superior to psychotherapy alone among the childhood abuse cohort. This clearly has implications for managing depression in the context of maltreatment. In fact, this is one of the strongest arguments for defining early life stress disorder as a distinct entity. Without definitions and codification, the implications of research findings will not be well translated, either for research or for clinical purposes. We do not have knowledge of many aspects of this entity. That is, we do not know what the early features are, or what the gene/environment interaction is. For example, catechol-O-methyl trasferase (COMT) variation has been implicated in predilection to violence in the context of trauma and serotonin transporter genetic variation to depression with the same context, ie, depending on the genetic background, stress produces a different expression.37 It is likely that clinical features of this entity will not be just syndromal depression or symptoms of PTSD but likely will include anxiety, aggression, and other fea-
tures not typically considered in the current DSM context or labeled as comorbidity.

**Why the need to define early life stress disorder as an entity?**

The reason for calling a particular feature an entity brings focus and attention. Thus, instead of evaluating patients with depression and stating that a high proportion suffered from trauma, and then stating that they have high comorbidity etc, it reverses the focus and the thinking pattern to a potential cause and the varied manifestations of that cause. By implication, this can lead to a focused search for understanding biology, better assessment of risk prognosis, genetic and social factors, and thereby better treatment and prevention. Given the high estimated rates of this condition, such a focus is imperative at both the research and clinical ends.

**Vascular depression**

The concept of vascular depression and its potential labeling gives us cause to reflect on the state of labeling psychiatric disorders and the challenges that lie ahead. The concept of vascular depression is not a new idea. Gaupp (1905) as quoted by F. Post described elderly patients with depression secondary to arteriosclerosis. Many had persistent apathy and depressed mood. These early findings were based purely on clinical evidence of cerebral vascular lesions, typically strokes. Magnetic resonance imaging (MRI) and other imaging techniques have allowed depiction of subtle but surprisingly widespread structural brain change in vivo.

Our group and others have previously introduced the notion of vascular depression (we initially used the term arteriosclerotic depression), and more precisely subcortical ischemic depression (SID). The broader definition of vascular depression encompasses both depression related to stroke and cardiac disease, and perhaps even hypertension. SID describes a more specific process, is analogous to a recent description of subcortical ischemic vascular dementia, and is similar to what has previously been termed MRI-defined vascular depression. We proposed that diagnostic criteria may be more specific to this entity than the more broadly defined vascular depression. The clinical syndrome meets requirements for diagnostic validity. SID has a clinical description, can be identified through laboratory studies (MRI), can be delimited from other disorders, is not associated with familial factors (for depression), and the changes seen on MRI can influence outcomes longitudinally. The supporting evidence includes the following points. Deep white matter and subcortical lesions as evidence of ischemic disease are more common in elderly depressed patients than healthy elderly control subjects. This has also been demonstrated in community populations. Family history of mental illness is significantly less common amongst these patients compared with those without these MRI changes. Large prospective studies have shown that subcortical lesions may be associated with persistence or worsening of depressive symptoms over time. There have also been preliminary studies associating new onset of depression with worsening subcortical disease, and worsening of lesion severity is associated with poor depression outcomes. There is also evidence of pathophysiological and neuroanatomical specificity, wherein lesions contributing to depression occur in the basal ganglia and frontal regions. The ischemic nature of these lesions has also been shown, and supports data associating severity of subcortical lesions with vascular risk factors such as hypertension, and the development of late-onset depression with a history of hypertension. This description of vascular depression can be incorporated into our current nomenclature system. We took an existing entity, major depression, and developed additional requirements specifying the criteria needed to call it vascular depression or subcortical ischemic vascular depression (SIVD). One significant limitation of this nominalist approach is that it circumscribes the definition to a previously described phenomenon, and presumes that the depression related to this disease process is akin to that noted in the previously described criteria. This approach, although initially useful, is limiting and incomplete. It does not reflect the fact that the disease process is complex, and therefore can manifest with not just lower grades of depression, but also other phenomena including cognitive impairment, dementia psychoses, and possibly mania at some point during the process and in some cases concurrently. The danger is illustrated by the tale of the five blind men and their description of the elephant. The same entity is described in different ways, based on the vantage point. The other approach would be to recognize subcortical ischemic vascular disease as the disease entity (see ref 58). Mood disturbances associated with SID may clearly include the full criteria for major depression, bipolar disorder, or dysthymia. In
addition, less severe or chronic mood disturbances are likely associated with subcortical ischemia; however, with the exception of International Classification of Diseases (ICD) minor depression, our current diagnostic nomenclature does not well capture these other disturbances. Other manifestations of SID include mild cognitive impairment, dementia, stroke, falls, and psychoses. Thus, labeling SID as the disease changes the emphasis to a disease process and therefore brings into focus the treatment of the disease process, recognizing varying manifestations and progression, for example, from mild cognitive impairment and/or depression to dementia. This focus now allows for the exploration of the causes of the disease process, and thereby enhances the likelihood of developing treatments that are more specific. This process has started for this entity from a neurological and geriatric medicine perspective. The varied clinical symptoms expressed will obviously need symptomatic treatment as is the case for depression, anxiety, mania, or dementia. This will allow the development of trials specific to this population, to assess the response patterns and suitability of different treatment approaches. This focus also allows the development of treatment and prevention approaches aimed towards the underlying causes. In the case of SID the causes are likely to be manifold in most instances. In some cases there may be just one cause, for example cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). When the cause is identified, i.e., CADASIL due to Notch 3 mutation, then the primary disease entity should be the causal entity. This is an example where the labeling moves from symptom to disease process and eventually to a causal level. As psychiatry moves from a purely phenomenological symptom course-based approach and follows the trends in medicine, our nomenclature will have to move toward a disease process and/or causally based nomenclature. The time for this change appears to be rapidly approaching. At this time, research is suggesting that some genes are risk factors for what have until now been regarded as unrelated syndromes. Most patients with psychiatric disease may have many attributable causes; in that case, common disease process-based descriptions will need to be developed, just as in the case of SIVD.

**Conclusion**

I have used two conditions to suggest a potential new taxonomy for depression. The one striking aspect of defining it on this basis is dropping the word “comorbidity” in this context. When we classify using a non-nominalist approach, the basic terminology is altered. Common co-occurrence of disorders gives us clues that could be helpful in looking for antecedents, and at the same time tell us that perhaps our current method is blinding our vision. As we open our eyes and look at emerging data in a nonbiased light, other conditions will emerge that could be useful in conveying information and treating patients. One cautionary note is the danger of overinterpreting genetic information. As potential genes at risk for one or more depressive disorders are identified and developed, defining the level of harm attributable to the gene is important, because any behavior associated with a genetic abnormality is in danger of being construed as disease-associated. This can overemphasize the genetic contribution of any one gene to disease etiology, and may lexicalize behavior patterns with unfortunate consequences. Patients with a genetic variation who are at minimal or no increased risk for adverse consequences should not be labeled as diseased. If the definition of disease is based solely on a genetic abnormality rather than on a clear specification of the risk, the label may harm the patient.
Hacia una taxonomía científica de la depresión

Dentro de la clasificación de la depresión se han introducido muchos conceptos, incluyendo el trastorno depresivo maniacodepresivo/bipolar, etc. El concepto original de Kraepelin de trastorno maniaco-depresivo ha evolucionado hacia el concepto de polaridad en el trastorno bipolar y unipolar. La clasificación psiquiátrica está caracterizada por una inflación de las categorías diagnósticas, incluyendo diversos subtipos de depresión. Este rápido efecto multiplicador es primariamente descriptivo y es necesario repensar de una manera pragmática el sistema de clasificación, en orden a desarrollar alguno que se espera sea útil y que cuente con bases científicas. ¿Es ahora el momento adecuado para preguntarse si existen condiciones de base que puedan ser relevantes para la depresión? Yo pienso que sí, y aquí yo introduciré esta noción con dos de estas condiciones. La primera es el trastorno por estrés precoz en la vida, y la segunda es la depresión vascular. Estas condiciones han alcanzado un nivel en que los datos obtenidos las sustentan como entidades distintas. En este artículo se discuten los fundamentos de esto.

13. Taylor WD, Steffens DC, Krishnan KR. Psychiatric disease in the twenty-first century: The case for subcortical ischemic depression. Biol Psychiatry. 2006;60:1299-1303.
14. Margolin G, Gordis EB. The effects of family and community violence on children. Annu Rev Psychol. 2000;51:445-479.
15. Agid O, Kohn Y, Lerer B. Environmental stress and psychiatric illness. Biomed Pharmacother. 2000;54:135-141.
16. Sedlack AJ, Broadhurst DD. Third National Incidence Study of Child Abuse and Neglect. Washington, DC: U.S. Government Printing Office; 1996.
17. Fumaluro R, Kinscherff R, Fenton T. Psychiatric diagnoses of maltreated children: preliminary findings. J Am Acad Child Adolesc Psychiatry. 1992;31:863-867.
18. Pelcovitz D, Kaplan S, Goldenberg B, Mandel F, Lehane J, Guerrera J. Post-traumatic stress disorder in physically abused adolescents. J Am Acad Child Adolesc Psychiatry. 1994;33:305-312.
19. McCauley J, Kern DE, Kolodner K, et al. Clinical characteristics of women with a history of childhood abuse. JAMA. 1997;277:1362-1368.
20. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14:245-258.
21. Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. The long-term impact of the physical, emotional, and sexual abuse of children: a community study. Child Abuse Negl. 1996;20:7-21.
22. Noorikajavi M, Afghah S, Dadkhah A, Holakoyie K, Motamedi SH. The effect of “parental loss” under 18 on developing “MDD” in adult age. Int J Psychiatry Med. 2007;37:347-355.

Vers une taxonomie scientifique de la dépression

La classification de la dépression inclut de nombreuses notions, dont celles de troubles maniaques/dépression bipolaire etc. Le concept original de trouble maniacodépressif de Kraepelin a évolué vers l’idée de polarité, et de troubles unipolaire ou bipolaires. La classification psychiatrique se caractérise par l’inflation de différentes catégories diagnostiques comme celle des sous-types de dépression, cet effet multiplicateur étant essentiellement descriptif. Le système de classification doit être repensé de façon pragmatique sur des bases scientifiques afin de pouvoir être utile. Est-ce le bon moment pour se demander si certains états pathologiques sont essentiels dans la dépression ? Je pense que oui, et je vais le démontrer avec deux exemples : le premier est le stress précoce en début de vie, et le second est la dépression vasculaire, deux manifestations considérées par les données comme des entités distinctes. Cet article propose la démonstration des deux exemples.

23. Carlson M, Earls F. Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. Ann N Y Acad Sci. 1997;807:419-428.
24. Goenjian AK, Yehuda R, Pynoo RS, et al. Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry. 1996;153:929-934.
25. Hart J, Gunnar M, Cicchetti D. Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. Dev Psychopathology. 1995;7:11-26.
26. Kaufman J, Birmaher B, Perel J, et al. Serotonergic functioning in depressed abused children: clinical and familial correlates. Biol Psychiatry. 1998;44:973-981.
27. DeBells MD, Keshavan MS, Clark DB, et al. A.E. Bennett Research Award. Developmental traumatology: Part II: Brain development. Biol Psychiatry. 1999;45:1271-1284.
28. DeBells MD, Keshavan MS, Spencer S, Hall J. N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. Am J Psychiatry. 2000;157:1175-1177.
29. Lemieux AM, Cole CL. Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. Psychosom Med. 1995;57:105-115.
30. Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatry. 2000;61:14-21.
31. Breier A, Kelsoe Jr. JR, Kinwin PD, Beller SA, Wolcott DM, Pickar D. Early parental loss and development of adult psychopathology. Arch Gen Psychiatry. 1988;45:987-993.
32. Stein MB, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol Psychiatry. 1997;42:680-686.
33. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000;284:592-597.
34. Luecken, LJ. Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. Psychosom Med. 1998;60:765-772.
35. Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry. 1997;41:23-32.
36. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000;342:1462-1470.
37. Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci. 2006;7:583-590.
38. Post F. The Significance of Affective Symptoms in Old Age: a Follow-Up Study of One Hundred Patients. Institute of Psychiatry, Mudsley Monographs No. 10. London, UK: Oxford University Press, 1962.
39. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997;154:497-501.
40. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. ‘Vascular depression’ hypothesis. Arch Gen Psychiatry. 1997;54:915-922.
41. Krishnan KRR, McDonald WM. Arteriosclerotic depression. Med Hypotheses. 1995;44:111-115.
42. Chui H. Dementia due to subcortical ischemic vascular disease. Clin Cornerstone. 2001;3:40-51.
43. Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry. 1998;42:705-712.
44. Taylor WD, Steffens DC, MacFall JR, et al. White matter hyperintensity progression and late-life depression outcomes. Arch Gen Psychiatry. 2003;60:1090-1096.
45. Coffey CE, Figiel GS, Djang WT, Weiner RD. Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. Am J Psychiatry. 1990;147:187-189.
46. Krishnan KRR, McDonald WM, Doraiswamy PM, et al. Neuroanatomical substrates of depression in the elderly. Eur Arch Psychiatry Clin Neurosci. 1993;243:41-46.
47. Tupilv LA, Krishnan KRR, McDonald WM, D’Souza S, Steffens DC. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. J Psychosom Res. 2002;53:665-676.
48. Steffens DC, Helms MJ, Krishnan KRR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. Stroke. 1999;30:2159-2166.
49. Steffens DC, Krishnan KRR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke. 2002;33:1636-1644.
50. Nebes RD, Reynolds CF, Boada F, et al. Longitudinal increase in the volume of white matter hyperintensities in late-onset depression. Int J Geriatr Psychiatry. 2002;17:526-530.
51. Lesser IM, Hill-Gutierrez E, Miller BL, Boone KB. Late-onset depression with white matter lesions. Psychosomatics. 1993;34:364-367.
52. MacFall JR, Payne ME, Provenzale JM, Krishnan KRR. Medial orbital frontal lesions in late-onset depression. Biol Psychiatry. 2001;49:803-806.
53. Greenwald BS, Kramer-Ginsberg E, Krishnan KRR, Ashtari M, Auerbach C, Patel M. Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. Stroke. 1998;29:613-617.
54. Thomas AJ, O’Brien JT, Davis S, et al. Ischemic basis for deep white matter hyperintensities in major depression. Arch Gen Psychiatry. 2002;59:785-792.
55. Liao D, Cooper L, Cai J, Toole JF, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: The ARIC study. Stroke. 1996;27:2262-2270.
56. Dufouil C, de Kersaint-Gilly A, Besancon V, et al. Longitudinal study of blood pressure and white matter hyperintensities. Neurology. 2001;56:921-926.
57. Lavretsky H, Lesser IM, Wohl M, Miller BL. Relationship of age, age at onset, and sex to depression in older adults. Am J Geriatr Psychiatry. 1998;6:248-256.
58. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging. 2002;23:421-431.
59. McDonald WM, Tupilv LA, Marsteller FA, et al. Hyperintense lesions on magnetic resonance images in bipolar disorder. Biol Psychiatry. 1999;45:965-971.
60. Finsterer J. Neuromuscular implications in CADASIL. Cerebrovasc Dis. 2003;24:401-404.