

Depression in adolescents and young adults with cancer

Eliza M. Park, MD; Donald L. Rosenstein, MD



Adolescents and young adults (AYAs) with cancer are at risk for depression due to disruptions in their developmental trajectory, greater physical symptom burden, and increased likelihood of developing aggressive disease. Rates of depression and other psychological disorders are substantially higher in AYAs with cancer when compared with older adults. Psychiatrists caring for these patients must consider the age-appropriate developmental context of these patients along with familial and medical factors that may influence the presentation and treatment of depression. Previous research suggests that psychosocial interventions specifically designed for AYA patients are promising, but studies of psychopharmacology treatments for depression are lacking. There is a pressing need for prospective studies and controlled clinical trials that evaluate the optimal strategies for treating depression in this patient group.

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Dialogues Clin Neurosci. 2015;17:171-180.

Keywords: *cancer; adolescent; young adult; depression*

Introduction

Cancer and depression, considered separately, are responsible for enormous human suffering on a global scale. An estimated 169 million years of healthy life were lost due to cancer worldwide in 2008,¹ and the World Health Organization (WHO) predicts that unipolar major depression will be the leading cause of disease burden by the year 2030.² When cancer and depression are comorbid, symptom burden and mortality are each magnified, as one disease complicates the management of the other. These challenges are particularly salient for adolescents and young adults (AYA), who have experienced increasing rates of both cancer and depressive disorders.^{3,4}

Although most cancer patients are elderly, the incidence of cancer in the AYA population continues to rise. These younger patients have unique psychosocial problems, including depression, and often require sophisticated clinical management.⁵ Despite these difficulties, the scientific literature on the optimal psychiatric care of depression in AYA cancer patients is noticeably scarce.

Author affiliations: Department of Psychiatry (Eliza M. Park, Donald L. Rosenstein) and Department of Medicine (Donald L. Rosenstein), University of North Carolina, Chapel Hill, North Carolina, USA

Address for correspondence: Eliza M. Park, MD, Department of Psychiatry, University of North Carolina, 170 Manning Drive, Campus Box #7305, Chapel Hill, NC 27599, USA
(e-mail: leeza_park@med.unc.edu)

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The treatment of depression in patients with cancer is relevant to psychiatrists due to the frequency of mood disorders in this population and the negative consequences of untreated depression on their medical and quality of life outcomes. For several reasons, oncology providers are becoming increasingly cognizant of the need to identify depression in their patients and referring them for psychiatric consultation. One important driver of this trend in the United States is the recent regulatory initiative of the American College of Surgeons Commission on Cancer, which mandates systematic psychosocial distress screening within accredited cancer programs.⁶ As this new culture of distress screening in oncology settings expands, we predict that substantially greater numbers of suspected depressed cancer patients will present for evaluation and treatment. Given the many challenges of patients with comorbid cancer and psychiatric illness, depression management of these patients requires psychiatric clinicians who can competently care for medically complex patients. As increasing numbers of AYA cancer patients with depression are identified, more research on optimal treatment will become necessary.

This review addresses important psychosocial and biomedical factors that are relevant to the diagnosis and treatment of depression in AYAs with cancer. We focus on the AYA population in active cancer treatment as well as AYA patients in cancer survivorship, due to the prevalence and importance of psychiatric disorders in both phases of the cancer continuum of care.

Cancer in adolescents and young adults

Defining the AYA population in cancer care has been difficult, as a number of different age ranges have been used in published studies. Most clinical investigators and organizations, including the National Cancer Institute, consider the AYA population to include individuals between the ages of 15 and 39.⁴ Within the United States, there are nearly 70 000 AYA patients diagnosed with cancer each year and tens of thousands of additional AYA individuals who complete cancer treatment annually.⁴ These estimates do not include the large number of individuals who survived a pediatric oncology illness that was diagnosed under age 15, though it should be noted that a diagnosis of cancer is six times more likely in adolescents and young adults than it is in children ages 0 to 14.⁴ The long-term psychiatric consequences

of childhood cancer survivors have been extensively studied and are both complex and beyond the scope of this review.^{7,8}

Innovations in cancer care have led to dramatically improved survival rates for both young children and older adults with cancer. Improvements have been less robust for younger adults with cancer. In the United States, cancer remains the leading cause of disease-related death in the AYA population, outpaced only by death due to accidents, suicide, and homicide. Among individuals with acute lymphocytic leukemia, AYAs have 5-year survival rates of 50% as compared with 80% among children.⁹ Across all cancer types, the annual rate of improvement in 5-year survival for AYAs has been less promising, particularly for individuals with breast cancer and leukemias.^{10,11}

Evidence also suggests that the underlying cancer biology may be different in younger versus older adults. Young adults disproportionately develop certain cancers—primarily lymphomas and leukemias, invasive skin cancer, genital tract malignancies, endocrine cancers, brain and spinal cord tumors, and breast cancer.^{10,12} They may also be more likely to present with advanced stage and aggressive disease, possibly due to inadequate insurance status, higher treatment burden, and limited treatment options.¹³ Compared with older women with breast cancer, young women are more likely to develop triple-negative basal-cell breast cancer, an aggressive form of the disease. In contrast to the overall decreasing rates of colorectal cancer incidence in the United States, rates of this diagnosis (as well as poorer outcomes) have actually increased among the AYA population.^{14,15}

AYA cancer patients also report higher symptom burden compared with older adults with the same cancer type. For example, younger women receiving chemotherapy endorse worse physical symptoms (eg, greater nausea and vomiting).¹⁶ Furthermore, multiple studies have demonstrated that younger age is associated with greater cancer pain throughout all phases of cancer—active treatment, survivorship, and advanced or incurable disease.¹⁷⁻²¹ Pain itself is associated with depression, and there likely exists a bidirectional relationship between greater pain symptoms and depression in the AYA cancer population.²² More broadly across all cancers, AYA patients report greater concerns about body image and sexuality; fertility concerns; and cognitive dysfunction,²³ along with evidence

of more negative changes in quality of life and subjective distress.²⁴

Depression in AYA patients with cancer

Epidemiology

Among all individuals with cancer, psychiatric syndromes are common.²⁵ Rates of adjustment disorders with depression or anxiety symptoms vary widely, with prevalence ranging from 16% to 42%.^{26,27} Estimates of minor depression or dysthymia are 20% in all cancer patients.²⁸ While imprecise, rates of all mood disorders are substantially higher among cancer patients than in the general population, with MDD occurring up to three times more frequently in cancer patients.²⁹ Although prevalence rates vary depending on the methodology employed, recent large and rigorously conducted studies in Europe estimate the point prevalence of major depressive disorder (MDD) between 5% and 15% depending on the site of cancer.^{30,31} In comparison, a systematic review of community-representative studies suggests a global point prevalence of MDD of 4.7%.³² In the United States, results from the National Comorbidity Survey Replication, a nationally representative survey using an expanded version of the WHO's Composite International Diagnostic Interview to assess mental disorders, estimated the 12-month prevalence of MDD as 6.6% in adults.³³

Younger age is consistently associated with higher rates of psychological distress and psychiatric syndromes in adults with cancer.^{34,35} However, specific differences in rates of depression between AYA and non-AYA cancer populations are varied due to differences in how cases of depression are identified in studies. One study that utilized data from the 2009 US population-based Behavioral Risk Factor Surveillance System, which included AYA cancer survivors and non-cancer controls, reported that AYA cancer survivors reported poorer mental health twice as frequently as AYAs without cancer.³⁶ A recent Danish cancer registry study reported substantially higher rates of hospitalization for depression in patients diagnosed with cancer compared with the cancer-free population. Patients 15 years and older were at highest risk for depression severe enough to warrant hospitalization within the first year following a cancer diagnosis, and remained at elevated risk in subsequent years.³⁷

Clinical presentation

Accurate estimates of depressive disorders occurring with cancer are difficult, in part, because of the diagnostic challenges in this group. The co-occurrence of physical symptoms such as fatigue, anorexia, and sleep disruption are common sequelae of an underlying malignancy or its treatment.³⁸ Whether and how these somatic symptoms should be considered in the diagnosis of a depressive disorder remains a subject of debate. In addition, common perceptions among providers and patients that depression is an "expected" response to a cancer diagnosis or a life-limiting illness further obscures accurate measurement of the prevalence of depression.

There are several cancer-specific considerations that may influence the accurate and timely diagnosis of depression in the AYA patient. Fatigue is one of the most common adverse effects of cancer therapy and can persist for years after treatment completion. Among long-term cancer survivors, younger age is more frequently associated with this adverse effect.³⁹ Fatigue is also the most commonly reported somatic symptom among patients with depressive disorders who present to primary care providers. In a pan-European study of 1884 individuals, fatigue was as frequently reported as depressed mood among men and women who were currently depressed.⁴⁰

Endocrinopathies not typically seen in AYA patients without cancer are not uncommon in patients with cancer, and frequently present with comorbid neuropsychological symptoms. Consequently, treatment of the underlying endocrine disorder may lead to modifications in standard antidepressant regimens (see treatment section, below). Among young women with breast and gynecological malignancies, many will experience chemical or surgical menopause due to treatment. Those with estrogen or progesterone receptor-positive tumors can expect chronic treatment with selective estrogen receptor modulators (tamoxifen) or aromatase inhibitors, which lead to reduction of estrogen in target tissues. Both classes of medications require long-term adherence to daily treatment and are associated with a variety of psychological, cognitive, and physical symptoms.^{41,42} Menopause itself is associated with a two- to fourfold increased risk of developing MDD, particularly among those with vasomotor symptoms⁴³ and sleep disruption.⁴⁴

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Among men with testicular and prostate cancers, androgen deprivation therapy is associated with a variety of mood effects including affective lability, irritability, sleep disturbance, and fatigue. AYA patients who are survivors of prostate or testicular cancer with low testosterone levels are at elevated risk for depressive disorders, though the data are equivocal regarding whether this is due to deficient testosterone or from the cancer and its treatment.⁴⁵ In addition, chronic opioid therapy—commonly prescribed for AYA patients in active cancer treatment or survivorship—can lead to opioid-induced androgen deficiency (OPIAD). Higher doses (ie, 100 mg or more of oral morphine equivalents daily) may be more likely to induce hypogonadism, though all patients receiving chronic opioid therapy are at risk.⁴⁶

Hypothyroidism is a risk for AYA patients exposed to therapeutic doses of radiation to the cervical neck region. This complication includes patients with head and neck cancers, lymphomas, and cancers of the central nervous system. Thyroid dysfunction may also occur in AYA patients with histories of breast cancer treated with loco-regional radiation therapy.⁴⁷ Although reported incidence rates vary widely, it is estimated that 20% to 30% of patients with histories of cervical neck radiation exposure are at risk of developing hypothyroidism, with peak occurrence during the first 2 to 3 years after completing therapy.⁴⁸ The psychological symptoms of hypothyroidism are well known to psychiatrists, and any AYA cancer patient who received radiation and presents with depressive symptoms merits thyroid function testing.⁴⁹

Patients who receive endocrine therapies, as well as those receiving any cytotoxic chemotherapy, commonly report chemotherapy-related cognitive symptoms. However, the magnitude of this effect is unclear, and treatment for these symptoms is not specific to cancer. Most studies utilizing formal neuropsychologic testing demonstrate a small-to-moderate negative impact on cognitive function in patients with chemotherapy exposure as compared with healthy controls.⁵⁰ Although chemotherapy-induced cognitive changes are often subtle, they may influence an individual's ability to maintain focus, organization, and memory, which can significantly impact quality of life as well as mood.⁵¹

There are also a growing number of cancer patients living with metastatic or incurable disease, and although estimates of the number of individuals in this group are

unknown, they are expected to increase as advances in cancer treatment allow patients to live longer with incurable illness. For example, the 5-year survival rate for metastatic breast cancer, an incurable disease, has more than doubled over the past 30 years.⁵² Unsurprisingly, the physical symptom burden is higher among patients with metastatic or other advanced cancers than in those who have completed cancer therapy.⁵³ In a systematic review of somatic and emotional symptom prevalence of 25 074 patients with incurable cancer, the most common symptoms reported were fatigue, pain, lack of energy, weakness, and appetite loss, which occurred in more than half of the sample.⁵⁴ Many of these symptoms overlap with diagnostic criteria for MDD, which interferes with accurate diagnosis in these clinical samples. Compounding these physical and affective symptoms is the burden of living with the existential threat of a shortened life. For patients just embarking on adulthood or in the prime of their family and work lives, the fear of cancer progression or recurrence can fundamentally color all aspects of their experience.

Developmental disruptions

Young adults with cancer experience disruptions in their normal developmental trajectory. Whether the cancer is diagnosed during advanced school years, an early career transition, or the start of a family, interruptions in expected life roles and responsibilities are major sources of psychological, practical, and existential concern for these patients and contribute to depression. The developmental theorist, Erik Erikson, postulated that the two main developmental tasks for the AYA population are: Identity versus Role Confusion (13-19 years); and Intimacy and Solidarity versus Isolation (20 to 39 years). During adolescence, individuals struggle to develop their identity. Peer relationships and social interactions become the predominant activities during this stage. As individuals mature into young adults, significant friendships and romantic relationships become the defining features of development. Young adults who are successful are able to form stable, long-lasting, mutually caring relationships. Those who are unsuccessful with this task are at risk for feeling isolated, lonely, and depressed.⁵⁵

AYA patients diagnosed with cancer frequently confront the loss of an imagined future for themselves that can, in turn, precipitate a grief reaction regarding cur-

rent and anticipated cancer-related losses. These losses often include the ability to bear biological children and delays in achieving other core developmental milestones. Serious medical illness often requires increased dependence from others after reaching previously achieved developmental tasks, conformity to medical or caregiver expectations, and social isolation from peers, all of which can directly challenge the need to establish autonomy and identity in older adolescents. Among young adults, a life-threatening illness threatens the establishment or maintenance of romantic relationships. For both adolescents and young adults, concerns about cancer recurrence, long-term treatment side effects (eg, sexual dysfunction, infertility, body image changes, financial and occupational difficulties, and disruptions to peer and romantic relationships) may have disproportionate psychological effects.⁵⁶

Barriers to treatment

Most cancer patients with depression do not receive appropriate treatment for their mood disorder. A failure to appreciate the impact of depression on cancer care, ambiguity in diagnosis, and lack of access to appropriate mental health services all contribute to this gap in care.^{57,58} Among AYA cancer patients, there are additional practical barriers that interfere with optimal depression management. These patients are less likely to receive medical care in the traditional primary care system where most patients without cancer receive treatment for their depression.⁵⁹ Among all age groups, AYAs are less likely to have insurance and report lower earnings than other adults.⁶⁰ Compared with adults without histories of cancer, AYA survivors are more likely to experience financial barriers and have low confidence in managing their survivorship needs.^{61,62}

Consequences of untreated depression

Untreated depression causes profound psychological suffering and impairments in quality of life. In patients with cancer, depressive disorders are also associated with multiple adverse cancer-related medical outcomes including refusal of adjuvant cytotoxic treatment, longer hospital admissions, and poorer adherence to prescribed treatment regimens.⁶³⁻⁶⁷ Although not definitively established, several reports suggest that AYA cancer patients are less adherent to acute cancer treat-

ment and survivorship care as compared with children or older adults. While there are multiple reasons for this difference, one critical factor is the patient's developmentally appropriate, but at times counterproductive, desire for autonomy.^{68,69}

Depression itself appears to be an independent predictor of mortality in cancer patients. Three meta-analyses suggest a 19% to 34% increased rate of mortality in cancer patients with depression symptoms.⁷⁰⁻⁷² This finding of increased mortality in depressed cancer patients is likely multifactorial in etiology. However, one specific concern, suicide, merits further discussion.

Suicide risk in young adults with cancer

Cancer is a substantial risk factor for suicide. In a large cohort study based on the Swedish Population and Housing census, the relative risk of suicide within the first week of a cancer diagnosis was 12.6 as compared with all adult patients without a cancer; within the first year after diagnosis the relative risk was 3.1.⁷³ Although less well studied, long-term cancer survivors are also at elevated risk of suicide, with reports suggesting increased risk up to 8 to 10 years following the original cancer diagnosis.³

AYAs with cancer may be particularly susceptible to suicidal ideation and completed suicide. Self-inflicted injury represents the second most common cause of death among individuals, both with and without cancer, aged 15 to 34 worldwide.⁷⁴ In another cohort study of Swedish individuals, aged 15 to 30, a cancer diagnosis conferred a relative risk of 1.6 for suicidal behavior. The greatest period of risk occurred during the period most proximate to the initial cancer diagnosis.⁷⁵ Other studies of AYA patients, focused on US populations, found that a cancer diagnosis is associated with a fourfold increase in likelihood of suicide attempts in individuals ages 17 to 39 years. This association remained even after controlling for relevant variables such as alcohol use, depression, and demographic characteristics.⁷⁶

In a small study of young adults with advanced cancer, more than 1 in 5 patients reported suicidal ideation. Interestingly, patient-oncologist alliance was found to be the strongest protection against suicidal ideation as compared with mental health interventions such as psychotherapy, psychopharmacologic management, or support group participation.⁷⁷ These results suggest that distress and suicide screening among the medically ill

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(rather than just behavioral health patients), a recommendation from the United States Joint Commission, may improve detection of suicidality and therefore our ability to intervene in this at-risk population.⁷⁸

Family considerations

Family composition and dynamics play a more prominent role for the AYA cancer population. AYA patients may still be living with parents (or need to move back home) just when they are establishing important romantic relationships. Other AYA cancer patients are in the early stages of their own parenting and child-rearing. The parental role and responsibilities for these patients may be an important contributor to their elevated distress. Parents with cancer are concerned about the impact on their illness on their young families⁷⁹ and rates of depression among all parents with cancer are high.⁸⁰

Data on advanced cancer patients with dependent children suggest they are more vulnerable to psychological distress than similarly aged cancer patients without children. A longitudinal study of patients with advanced cancer found that parental status was associated with lower levels of peacefulness and having more worry as compared with nonparents. Their surviving spouse or caregivers also experienced significantly higher rates of depression, anxiety disorders, and complicated grief.⁸¹ While this study did not specifically evaluate AYA cancer patients who are parents, the parental group was on average, 13.4 years younger than the nonparents. Data from a sample of bereaved widowers with dependent-age children who lost a spouse to cancer indicate high levels of bereavement and depressive symptoms, even up to 2 years after the death of their wife.⁸² Multiple other studies have demonstrated the negative effect of a parental cancer diagnosis on minor children.^{83,84} In sum, the effects of a cancer diagnosis for parents of dependent children—a population that principally encompasses the AYA population—can have negative and long-term ramifications for the entire family.

Treatment of depression in AYA cancer patients

Psychosocial support and treatment

Existing interventions tailored specifically for the AYA population have focused on promoting achievement of

developmental tasks, maintaining a sense of identity, and improving peer support. Preliminary evidence suggests that peer support approaches may be more desirable among AYA cancer patients than family-based interventions.⁸⁵

The use of electronic and Internet media is common among AYA individuals. Consequently, Internet-based resources are common ways that AYA patients with cancer identify and maintain peer support. These resources can vary from generalized support and information, as can be found at Stupid Cancer (www.stupidcancer.org) and the Ulman Cancer Fund for Young Adults (<http://ulmanfund.org>), to Web sites focused on specific issues such as fertility, financial needs, and family concerns. There are also several disease- and geography-specific organizations for AYA cancer patients—particularly for those with breast cancer—that provide more tailored information, resources, and opportunities for social networking. Both formal and informal online communities, ranging from large organizations such as Planet Cancer (<http://myplanet.planetcancer.org>) to individual blogs and personal Web sites, provide peer-based support for AYA patients with cancer.

Despite the increasing interest in promoting the psychological well-being of AYA cancer patients and survivors, there remain large gaps in research and service delivery. Promising developments are exercise and activity-based resources such as First Descents (<https://firstdescents.org>) and Athletes for Cancer (www.athletes4cancer.org). While these interventions may be ideal for many cancer survivors, they remain less helpful for those individuals who cannot participate fully in physical-based interventions. Consequently, there is a pressing need for resources for young adults with incurable illness or profound functional limitations.

Psychopharmacologic approaches

There are several general references that address principles and strategies for the pharmacological management of depression in patients with cancer.^{27,29,49,86,87} Specific considerations for the AYA cancer population include therapies that minimize sexual dysfunction and, when possible, address comorbid somatic symptoms. Many AYA patients, both during active treatment and survivorship, remain on multiple other medications, and drug-drug interactions are highly relevant. For example, an average bone marrow transplant patient admitted to

the hospital receives 29 medications.⁸⁸ Specific somatic symptoms that are targets for psychotropic treatment in AYA cancer patients include peripheral neuropathy and other pain syndromes, fatigue, anorexia, and hot flashes. A targeted symptom-reduction approach is recommended for these patients with high medical complexity even if they do not meet full criteria for MDD. Clinical strategies that favor antidepressants with adverse effect profiles matched to patients' dominant cancer-related symptoms may be more appropriate for this group.^{89,90}

Specific agents that may work well for this population include the use of duloxetine to address depression and other pain syndromes, such as peripheral neuropathy or musculoskeletal pain from aromatase-inhibitors. Mirtazapine, an agent not commonly used in the noncancer AYA population, may be particularly helpful for treatment of weight loss, nausea, or insomnia. Venlafaxine is often used for treatment of comorbid depression and hot flashes, particularly in premenopausal women who suffer from hot flashes and for whom treatment with p450 2D6 inhibitors might compromise the efficacy and clinical benefits of tamoxifen.^{91,92} Although the clinical impact of 2D6 activity in women taking tamoxifen remains a subject of ongoing investigation,⁹³ a population-based cohort study suggests that the inhibition of the hepatic cytochrome p450 2D6 isoenzyme, which converts tamoxifen into

its active metabolite, endoxifen, with medications such as paroxetine may be associated with increased risk of death from breast cancer.⁹⁴

Conclusion

AYAs with cancer face multiple challenges to their emotional well-being that are distinct from those encountered by either younger or older patients with cancer. AYA patients remain an understudied and underserved population despite the increasing prevalence of AYA cancer worldwide. A particularly important concern for AYA patients is the development of MDD. Knowledge of the unique risk factors for depression in this age group is important for psychiatrists who will be encountering these patients in greater numbers in the future. Prospective studies and controlled clinical trials are needed to advance optimal strategies for treating depression in this patient group. For example, studies to clarify the clinical relevance of p450 2D6 antidepressant-mediated inhibition during tamoxifen treatment and the development of peer interventions for AYAs with advanced cancer and depression are sorely needed. Psychiatrists have a unique and important role in the care of AYA patients suffering from both cancer and depression. □

Disclosures: Drs Park and Rosenstein have no disclosures to report.

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Clinical research

La depresión en adolescentes y adultos jóvenes con cáncer

Los adolescentes y adultos jóvenes (AAj) con cáncer tienen un riesgo de depresión debido a las alteraciones en su trayectoria evolutiva, al mayor impacto de los síntomas físicos y al aumento de la probabilidad de desarrollar patologías con agresividad. Los porcentajes de depresión y otros trastornos psicológicos son significativamente mayores en los AAj con cáncer en comparación con los adultos mayores. Los psiquiatras que atienden a estos pacientes deben considerar el contexto del desarrollo apropiado a la edad de ellos junto con los factores familiares y médicos que pueden influir en la presentación y tratamiento de la depresión. La investigación previa sugiere que las intervenciones psicosociales diseñadas específicamente para los pacientes AAj son promisorias, pero faltan estudios de terapias psicofarmacológicas para la depresión. Existe una necesidad urgente de contar con estudios prospectivos y ensayos clínicos controlados que evalúen las estrategias óptimas para tratar la depresión en este grupo de pacientes.

Dépression chez les adolescents et les jeunes adultes cancéreux

Le risque de dépression chez les adolescents et les jeunes adultes cancéreux est dû aux perturbations de leur trajectoire de vie, au poids plus important de leurs symptômes physiques et à la probabilité plus élevée de développer une maladie agressive. Chez eux, les taux de dépression et des autres troubles psychologiques sont considérablement plus élevés que chez les adultes plus âgés. Les psychiatres qui s'en occupent doivent prendre en compte le contexte de leur développement selon leur âge, parallèlement aux facteurs familiaux et médicaux pouvant influir sur la présentation et le traitement de la dépression. D'après des recherches antérieures, des procédures psychosociales spécifiquement programmées pour ces patients sont prometteuses, mais il manque des études sur les traitements psychopharmacologiques de la dépression. Il faut absolument des études prospectives et des essais cliniques contrôlés pouvant évaluer les stratégies optimales du traitement de la dépression dans ce groupe de patients.

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