AIDS PATIENT CARE and STDs
Volume 26, Number 11, 2012

DOI: 10.1089/apc.2012.0113

Treating Depression Within the HIV "Medical Home": A Guided Algorithm for Antidepressant Management by HIV Clinicians

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Abstract

People living with HIV/AIDS (PLWHA) suffer increased depression prevalence compared to the general population, which negatively impacts antiretroviral (ART) adherence and HIV-related outcomes leading to morbidity and mortality. Yet depression in this population often goes undiagnosed and untreated. The current project sought to design an evidence-based approach to integrate depression care in HIV clinics. The model chosen, measurement-based care (MBC), is based on existing guidelines and the largest randomized trial of depression treatment. MBC was adapted to clinical realities of HIV care for use in a randomized controlled effectiveness trial of depression management at three academic HIV clinics. The adaptation accounts for drug–drug interactions critical to ongoing ART effectiveness and can be delivered by a multidisciplinary team of nonmental health providers. A treatment algorithm was developed that enables clinically supervised, nonphysician depression care managers (DCMs) to track and monitor antidepressant tolerability and treatment response while supporting nonpsychiatric prescribers with antidepressant choice and dosing. Quality of care is ensured through weekly supervision of DCMs by psychiatrists. Key areas of flexibility that have been important in implementation have included flexibility in timing of assessments, accommodation of divergence between algorithm recommendations and provider decisions, and accommodation of delays in implementing treatment plans. This adaptation of the MBC model to HIV care has accounted for critical antidepressant-antiretroviral interactions and facilitated the provision of quality antidepressant management within the HIV medical home.

Introduction

A meta-analysis of depression prevalence studies prior to the era of highly active antiretroviral therapy (HAART) estimated that HIV-infected individuals have double the prevalence of depression compared to the general population.[1] This increased prevalence among people living with HIV/AIDS (PLWHA) has continued in the HAART era[2–4] regardless of gender, ethnicity, sexual orientation, or comorbid substance abuse.[2,3,5–7] The co-occurrence of depression with HIV infection can negatively impact antiretroviral therapy (ART) adherence and virologic and immunologic outcomes[8–11] leading to increased AIDS-related morbidity and mortality.[11–15]

Observational studies suggest that among PLWHA with depression, those receiving depression treatment have higher CD4 counts, lower viral loads, and decreased mortality,[15] largely mediated through increased adherence to ART,[9,16–19] although randomized controlled trials are lacking. Despite the high prevalence of co-occurrence and known benefits of therapy, depression may often go undiagnosed[20] and untreated in PLWHA. Limited access to specialty mental health providers represents an important potential barrier to care for HIV-infected depressed patients.

A model referred to as measurement-based care (MBC) is a promising new paradigm to guide mental health care in areas where access is limited. The premise of MBC is that depressive symptoms and side effect burden are measured at regular intervals with a validated instrument and a predetermined sequence of antidepressant treatments (depression care algorithm) are offered based on the measures of symptom severity

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and tolerability. The goal is to achieve remission: few to no measurable depressive symptoms with return to baseline functioning. MBC offers evidence-based guidance on depression management in situations in which access to specialty mental health care is limited. With MBC, social workers, nurses, or other trained members of the health care team can measure symptoms and treatment response, assess tolerability, and provide decision support to nonpsychiatric prescribers based on the treatment algorithm. In this way, MBC provides a framework to safely and successfully manage depression in patients who otherwise may not receive this valuable care. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the largest trial of depression treatment, demonstrated that MBC can equip primary care settings to deliver depression treatment equivalent to that received in specialty psychiatric clinics.[21]

While successful in primary care clinic settings, MBC has not been tested in an HIV clinic. Recent data suggest that increased HIV survival, a benefit of the HAART era, leads to greater utilization of mental health services.[22] However, HIV clinics and the population receiving HIV care often have limited access to mental health professionals despite the high prevalence and co-occurrence of depression. HIV care providers often work in multidisciplinary clinics and provide many primary care services, making the HIV clinic an ideal "medical home" in which to utilize MBC as a way of meeting increasing mental health needs. Our purpose here is to describe the adaptation of MBC for use in three HIV specialty care clinics as preparation for a currently ongoing trial testing the effect of depression management on HIV medication adherence.

Principles of MBC

MBC is an evidence-based, resource-efficient depression management strategy designed to equip psychiatric and nonpsychiatric medical practitioners to deliver best-practices, guideline-concordant depression management. Consistent with principles of task-shifting and long-term disease management successfully applied to a range of chronic illnesses, MBC relies on a nonphysician depression care manager (DCM) to assess key metrics of depression treatment regularly and provide decision support to the treating physician regarding antidepressant initiation, dosing, and switching. The role of the DCM may be effectively filled by individuals with a range of training depending on the practice, including nurses or social workers, enhancing the adaptability of the model to a range of clinical settings.

Development. The foundation for the MBC model was developed in the Texas Medication Algorithm Project (TMAP) in 1996.[23] The TMAP approach[24] consists of: (1) evidence-based, consensually approved medication algorithms; (2) clinical and technical support necessary to allow the clinician to use the algorithm; (3) patient programs that allow the patient to be an active partner in care[25]; and (4) uniform documentation of care provision and patient outcomes. Its model has been quite successful for major depressive disorder in that patients have demonstrated greater depressive symptom reduction and improvement in the SF-12 mental health score compared to treatment as usual groups.[26]

MBC was further refined and extended for use in primary care medical settings in the design and implementation of STAR*D, the largest prospective trial of depression treatment ever conducted.[27,28] The goal of STAR*D was to determine which of several antidepressant algorithms produced the greatest likelihood of recovery for patients whose depression did not resolve with the first intervention. STAR*D deployed MBC in psychiatric and primary care settings, achieving equivalent rates of depression remission in both settings.[21] The demonstrated potential of MBC to support delivery of effective depression management in nonpsychiatric settings can mean higher access for many patients to quality depression care without the delay of referral to specialists. Infectious diseases physicians and extenders receive the same training in psychiatric diagnosis and treatment as do primary care providers. It is not expected that this basic education can provide ongoing expertise in an age of evolving treatment and diagnostic schema. As such, shifting this expertise to DCMs with psychiatric oversight is a rational means of ensuring best-practices principles are maintained while providing depression treatment for patients in these nonpsychiatric settings.

General principles. The MBC strategy for depression follows depression treatment guidelines[29–31] and is summarized in Figure 1 and the following principles:

1. *The goal of depression treatment is remission, not response.* Treatment should be adjusted until the patient has achieved full recovery with no residual depressive symptoms. Stabilizing or discontinuing treatment when the patient has improved (responded) but residual symptoms remain increases the risk of recurrence.[32]
2. *Assess depressive symptoms systematically.* Quantitative indicators and goals such as hemoglobin A_{1C} for patients with diabetes or blood pressure for patients with hypertension guide most chronic disease management approaches. Similarly, once depression has been diagnosed (using a diagnostic interview), treatment decisions for patients with depression should be guided by validated quantitative measures rather than non-systematic impression.[29,30] In the psychiatric field, the standard for assessment of depression treatment response is systematic self-report instruments, several of which have well-defined and validated ranges for determining treatment response and remission.[33]
3. *Monitor side effects early and often.* While serious toxicity from current first-line antidepressants is uncommon, discontinuation of treatment due to undesired side effects such as decreased libido or weight gain is a primary reason for antidepressant treatment failure.[34] Side effects should be regularly assessed so as to encourage patient adherence and promptly identify intolerable side effects that may be addressed or require switching antidepressants.
4. *Start low.* A low starting antidepressant dose often eases the introduction of side effects, allowing them to be addressed before they become intolerable.
5. *Increase dose to remission, using the full dosing range if needed.* Treatment response should be assessed after 4–8 weeks at a given dose. If insufficient improvement is seen, the dose should be increased until remission is achieved, side effects become intolerable, or the maximum approved dose has been reached.
6. *Ensure an adequate trial before switching or referring.* As long as any side effects remain tolerable, a patient

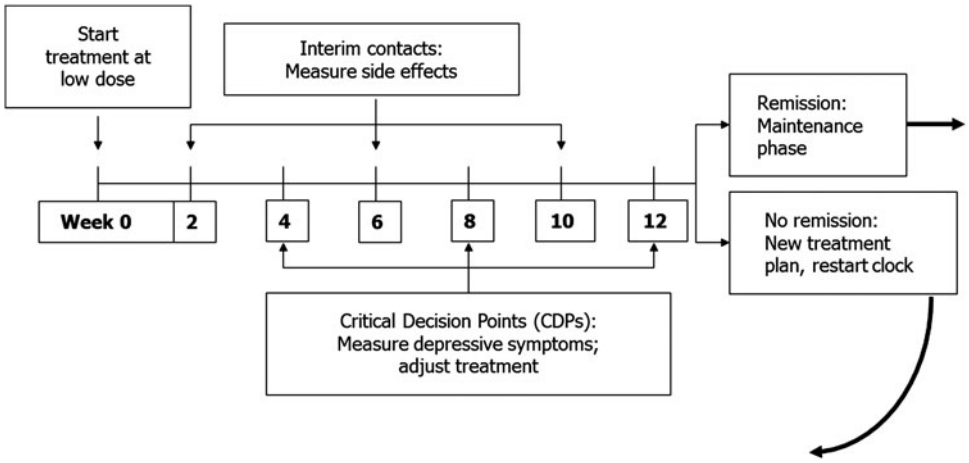

FIG. 1. Overview of measurement-based care timeline.

should receive an adequate trial of a medication (i.e., 8–12 weeks on a given medication, 4–6 of those weeks at moderate to high doses) before declaring a treatment failure and switching antidepressants or referring to specialty care.

Methods

Adaptation of MBC to HIV care

We adapted MBC for use with HIV patients as part of the groundwork for an NIH-funded study of the effect of depression treatment on ART adherence (Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, and UNC, or SLAM DUNC, R01-MH086362, ClinicalTrials.gov registry NCT01372605). The primary adaptation involved identification of specific antidepressants to include in the algorithm that would avoid potential drug-drug interactions with ART and treatments for common HIV-related conditions. We compiled a candidate list of antidepressants from those supported in nationally and internationally recognized expert consensus guidelines.[35–37] This list was compared via a drug-by-drug interaction review with all FDA-approved medications for HIV and common opportunistic infections as of February 2008 (updated May 2011; www.aidsinfo.nih.gov). The interaction review was conducted through a drug-interaction database[38] and a hand search of *in vivo* P450 enzyme data.[39] Only antidepressants identified by each method as being low risk for interaction were selected. Two independent psychiatrists experienced in treating depression in PLWHA then vetted this list.

Resulting antidepressants. The above process yielded six antidepressants (Table 1): citalopram, escitalopram, sertraline, bupropion, mirtazapine, and venlafaxine. Duloxetine was subsequently added based on its favorable drug interaction profile. Our review yielded no evidence that these antidepressants would either inhibit or potentiate the metabolism of any antiretroviral or HIV-related medication. While there is some evidence that certain antiretrovirals may potentiate[40] or inhibit[41] certain antidepressants, the most recent national guidelines do not recommend adjusting antidepressant starting doses based on the patient's ARV regimen.[41] Therefore, the algorithm recommends a common starting dose or range regardless of ARV regimen.

The algorithm

The adapted MBC algorithm reflects the general principles of MBC outlined above. The algorithm ensures antidepressant initiation at a low dose; early and regular assessment of side effects; systematic measurement of depressive symptoms; antidepressant dose increases at regular intervals until maximum dose reached, remission is achieved, or side effects become distressing; and an adequate trial of a given antidepressant at sufficient dose and duration to either achieve remission or declare treatment failure.

After the initial contact, the MBC timeline proceeds with critical decision points (CDP) every 4 weeks and interim contacts between each CDP (Fig. 1). Detailed decision trees for the initial and CDP contacts are shown in Figs. 2 and 3. After 12 weeks, or 3 CDPs, a regimen is declared either a success with the patient entering a maintenance phase, or a failure with a change in the treatment plan being made.

Initial contact (Fig. 2). The algorithm starts with determination by the DCM of the presence of a current major depressive episode that is not a bipolar or psychotic disorder utilizing a standard diagnostic instrument (in this case the Mini International Neuropsychiatric Interview).[42,43] The algorithm then recommends starting an antidepressant, the selection of which is the result of a pragmatic discussion between the patient, provider, and DCM. The selected antidepressants have comparable efficacy and research has not yet identified patient characteristics that predict a higher likelihood of response to one over another. Therefore, the choice is driven largely by previous response, side effect profile, or cost.

If the patient is already on an antidepressant but still has moderate to severe depressive symptoms (i.e., meets criteria for major depressive episode), the algorithm recommends maintaining the current dose if the patient has been at that dose less than 4 weeks. Otherwise, the algorithm suggests increasing the dose if applicable or switching to a new antidepressant if an adequate trial has been achieved or side effects are intolerable.

Critical decision points (Fig. 3). CDPs for possible treatment changes occur every 4 weeks. At these visits, the DCM reassesses depressive symptoms and side effects. Based on this assessment, the DCM makes a new treatment recommendation to the HIV clinician guided by the algorithm. If

Table 1. Antidepressants and Dosing Recommendations Included in HIV Adaptation of Measurement-Based Care

Medication	Generic available?	PAP available?	How to take	Principal side effects	Additional considerations	Dosing recommendations (mg)		
						Starting dose	Progression	Maximum
Citalopram	Yes	Yes	Anytime, usually in AM	Nausea Decreased libido	Nausea tends to resolve, decreased libido does not.	10–20 mg qd	(10→) 20→40→60[a]→80[a]	80[a] qd
Escitalopram	No	Yes	Anytime, usually in AM	Nausea Decreased libido	Nausea tends to resolve, decreased libido does not.	5–10 mg qd	(5→) 10→20→30→40	40 qd
Sertraline	Yes	Yes	Anytime, usually in AM	Nausea Decreased libido	Nausea tends to resolve, decreased libido does not.	25–50 mg qd	(25→) 50→100→150→200	200 qd
Mirtazapine	Yes	Yes	Take at night	Drowsiness Weight gain (~5 kg)	No sexual side effects. Often increases appetite. Can help with insomnia at lower doses (<30 mg). May help with decreased libido if added to an SSRI.	7.5–15 mg qd	(7.5→) 15→30→45→60	60 qd
Bupropion SR	Yes	Yes	Take in AM and early PM	Insomnia Activation/restlessness	No sexual or weight side effects. Can help if focus and concentration are a concern.	150 mg qd	150 qd→150 bid→200 bid	200 bid
Bupropion XL	No	Yes	Take in AM	Insomnia Activation/restlessness	May exacerbate agitated depression or comorbid anxiety. Can help with smoking cessation, and may help decrease craving in patients with substance abuse history. For patients with seizure history, may increase risk of seizure at higher doses.	150 mg qd	150 qd→300 qd→450 qd	450 qd
Venlafaxine XR	Yes	Yes	Take in AM	Insomnia Activation/restlessness	Side effects similar to SSRIs, especially at lower doses (initial nausea; decreased libido). Blood pressure should be monitored, especially at higher doses.	37.5–75 mg qd	(37.5→) 75→150→225→300→375	375 qd[b]

[a]Recent FDA evidence suggests greater risk of QT prolongation at doses >40 mg. EKG monitoring recommended above this dose range.
[b]Limited evidence for increased efficacy at doses >225 mg, but clinical trials and measurement-based care algorithms have safely and successfully dosed up to 375 mg.
PAP, Patient Assistance Program; RTV, ritonavir; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; qd, once daily; bid, twice daily.

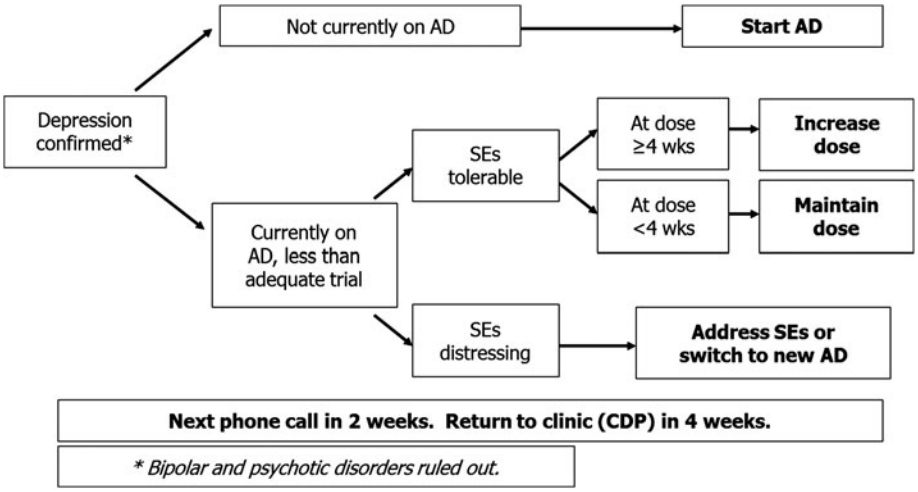

FIG. 2. Decision tree for initial clinical contact.

side effects are intolerable, the recommendation is to address them, reduce the antidepressant dose, or switch to a new antidepressant. If side effects are absent or tolerable, the recommendation is to maintain the dose for those who have remitted (PHQ-9 < 5), increase the dose for those who have moderate to severe depressive symptoms (PHQ-9 = 10–27), and increase or maintain the dose for those who have partial response (PHQ-9 = 5–9; maintaining the dose is favored if there had been substantial improvement in symptoms, increasing the dose would be favored if improvement had been small).

Interim contacts. These are brief contacts, usually conducted over the phone 2 weeks after baseline and each CDP, to assess side effects and provide encouragement. Generally no treatment change recommendation arises from these contacts unless distressing effects are noted.

Treatment success or failure. After 12 weeks (CDP 3), treatment is generally either declared a success or a failure. Patients who have achieved remission (PHQ-9 < 5) enter the maintenance phase with DCM contact every 2–3 months to confirm continued remission. If remission has not been achieved (i.e., treatment failure), the recommendation is to switch to or augment with another antidepressant. Optionally, the provider and patient may decide to extend the trial to a fourth CDP if remission is believed imminent and a positive trend has been detected. After two failed trials the recommendation is to refer for a psychiatric consultation.

The treatment team

MBC treatment of depression is an integrated, collaborative-care approach that involves the DCM, the prescribing provider, a supervising psychiatrist, and the patient. The distribution of tasks is meant to rationally divide the workload according to time demands and skill level.

The DCM. The DCM's role is to provide decision support to the prescribing (HIV) provider for depression treatment. The DCM has primary contact with the patient at each step in the algorithm, collects the standardized assessments of depressive symptom severity and side effect burden, and

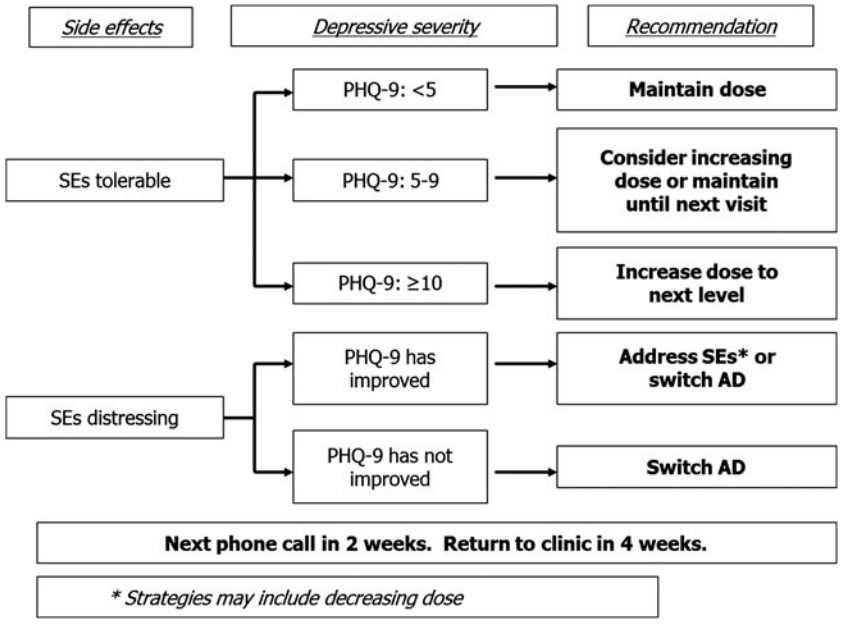

FIG. 3. Decision tree for follow-up clinical contacts.

consults the decision algorithm to determine the recommended treatment plan. The DCM summarizes this for the prescribing provider and provides specific recommendations or relative advantages of available options for the patient. With the patient, the DCM emphasizes the importance of treatment adherence and serves as a resource for questions about treatment. The DCM also probes for suicidal ideation at each contact, assesses severity of any suicidal ideation, and responds or refers appropriately.

The prescribing provider. In the MBC model, all final treatment decisions remain the purview of the prescribing provider (in this application, the HIV provider). The provider confirms the initial depression diagnosis, receives decision support about treatment from the DCM, discusses the treatment recommendation with the patient, and writes any resulting medication prescription.

The supervising psychiatrist. The supervising psychiatrist conducts weekly supervision with the DCM to review all patients contacted in the past week and to address any questions that arose regarding recommendations or treatment plans. The psychiatrist pays particular attention to whether the appropriate recommendation was made and instances in which the provider's plan or actual treatment implementation diverged from the recommended treatment plan and timeline. The psychiatrist is also available for *ad hoc* consultations about specific patients, treatment decisions, or urgent issues (e.g., suicidal ideation) as needed.

The patient. The patient is the central focus in the development and implementation of the treatment plan. His or her personal history and preferences will inform decisions made by the DCM and the prescribing provider. Barriers to treatment such as cost and side effects are critically important to understand and the patient is given every opportunity to share these with the treatment team. Understanding depression and its treatment can empower patients to participate in self-management by monitoring their symptoms, side effects, and treatment adherence and reporting these regularly to the DCM and provider. This results in patient-centered care that improves trust, communication, and adherence while improving quality of care and clinical outcomes.[44]

Results

The SLAM DUNC study began enrolling subjects in April 2010. As of May 15, 2012, 190 participants had enrolled, of whom 90 were randomly assigned to the MBC intervention. Per inclusion criteria, all had a diagnosis of major depressive disorder according to the Mini International Neuropsychiatric Interview (MINI). The frequency of comorbid anxiety disorders was 60.3% ($n=114$): 15.5% ($n=29$) with panic disorder, 22.1% ($n=42$) with PTSD, and 46.8% ($n=89$) with generalized anxiety disorder. Comorbid substance use disorders were present in 29.0% ($n=54$): 20.2% ($n=38$) with drug abuse or dependence and 24.2% ($n=45$) with alcohol use or dependence.

Prior to study launch, 96% of providers at the three sites (67/70) reported already prescribing antidepressant medications for their patients with suspected depression. While most (58%) were very or extremely confident starting an antidepressant, far fewer (14%) were comfortable with augmenting or switching antidepressants if the first trial was not successful.

Over the first 26 months of the study, DCMs have managed a mean active caseload of 6.2, 8.5, and 8.7 patients in the acute treatment phase at sites 1, 2, and 3, respectively, as well as a caseload of 8.5, 10.9, and 4.0 patients in the maintenance phase of treatment. DCMs held a mean of 2.5, 3.4, and 1.8 MBC contacts per week, respectively, at the three sites (overall mean number of contacts per DCM per week: 2.8; standard deviation [SD]: 1.8; range, 0–10). The psychiatric supervision team has reviewed a mean of 6.5 MBC encounters per week (SD: 3.0; range, 0–14).

Implementation process

Implementation of MBC has required flexibility in certain key areas. One such area has been timing and medium of contacts. In some cases implementation of a treatment plan is delayed, for example because the patient is applying for medication through a Patient Assistance Program, because of patient or provider delays in communicating a prescription to a pharmacy, or because of patient delay in starting to take a new medication or dose. In these cases the study team has delayed the CDP so that it occurs 4 weeks after the actual implementation of the new medication or dose, to allow sufficient time to measure response to the new treatment. If the delay is extended (>2 weeks), interim contacts are repeated biweekly to continue to monitor side effects and suicidality until the CDP. Since treatment decisions always remain in the hands of the provider, the algorithm must also accommodate treatment decisions that differ from the recommendation. The DCM advises based on the evidence before her, including the patient's depressive symptoms, tolerance of medications, and current ART and antidepressant regimen. The provider may have additional information about the patient's health status or likely adherence, or may have a different interpretation of interpersonal situations impacting the patient's mental status. It is not uncommon for a provider to forgo changing the treatment plan to see whether situational or health factors may resolve in a way that positively impacts depressive symptoms. When the provider's decision deviates from the algorithm recommendation, the DCM continues to monitor the participant as before until the next CDP, when the next discussion about treatment changes occurs. Relatedly, the provider and patient may decide they are content with an improvement in depressive symptoms (e.g., PHQ-9 in 5–9 range) that does not meet the algorithm criteria for remission (PHQ-9 <5). Although the algorithm may recommend additional treatment changes to achieve remission, the provider and patient may decide the current treatment plan is satisfactory. In this case the DCM enters the patient into the maintenance phase with less frequent monitoring to ensure continued response to the current treatment.

The algorithm also supports flexibility in choice of antidepressant medication. The medications listed in Table 1 are not the only antidepressants available. Prescriber and patient experiences with other medications have led the team to support providers' prescription of alternative antidepressants without formally endorsing them. For example, fluoxetine and paroxetine are efficacious antidepressants but have unfavorable metabolic or side effect profiles in combination with ART. For providers who select an alternative antidepressant, the DCM still plays the role of carefully monitoring response and tolerability. Gradual dose increases for alternative antidepressants must necessarily be determined by the supervising psychiatrist.

Discussion

We have described an adaptation of the proven MBC depression treatment model for application in HIV clinical care, including a careful evaluation of potential interactions between antiretroviral and antidepressant medications. The MBC model provides a roadmap for a team including an HIV provider, a DCM, and a supervising psychiatrist to provide best-practices, high-quality, resource-efficient antidepressant management within the HIV clinical setting.

Important lessons in processes of implementation have been described. As initially presented, the algorithm can appear straightforward and easily implemented, whereas in practice, some flexibility must accompany the process. The weekly supervision calls with the DCMs and supervising psychiatrists have played a critical role in accommodating needed flexibility while adhering to the underlying principles of MBC and maintaining high quality of care.

The population under study is admittedly a challenging one with multiple comorbidities including anxiety and substance use. While several first-line treatments for depression are likewise efficacious for anxiety-spectrum disorders, the algorithm does not directly or indirectly address comorbid substance use disorders. For such individuals, the proposed algorithm may become one part of a larger treatment plan with the goal of minimizing the impact of depression on treatment adherence and substance misuse.

This application of the MBC model is notable for supporting the provision of best-practices antidepressant management within the HIV clinical setting. The model applies a team approach to treatment decisions, in which the HIV provider retains final decision-making authority but receives decision support from a trained DCM, who in turn is supervised by a psychiatric specialist. Although lacking advanced psychiatric training, HIV providers receive the same training in principles of antidepressant prescription as primary care providers. The close and careful monitoring built into the MBC approach, delivered through decision support from the DCM and ongoing supervision by a psychiatric provider ensures that guideline-concordant care is being delivered.

The promise of MBC lies in its focus on equipping nonprescribing personnel with the expertise and supervision necessary to guide high-quality, best-practices antidepressant treatment, empowering nonpsychiatric clinicians such as HIV providers to safely and effectively manage depression in their patients. This model of task-shifting and concentration of services within the primary "medical home," as envisioned in the White House's National AIDS Strategy,[45] has the potential to address the widespread underdiagnosis and undertreatment of depression in HIV patients.

Acknowledgments

All authors meet ICMJE criteria for authorship. J.L.A., B.N.G., and B.W.P. conceived of the design; T.M., R.M., and J.W. contributed to the analysis and interpretation of the data. J.L.A., B.N.G., R.M., and B.W.P. drafted the manuscript; T.M. and J.W. revised the manuscript for important intellectual content. J.L.A., B.N.G., and B.W.P. obtained funding for the work, R.M. provided technical support, and T.M. and J.W. provided supervision. All authors agree with the manuscript's results and conclusions. B.W.P. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The SLAM DUNC study is supported by grant R01MH086362 of the National Institute of Mental Health and the National Institute for Nursing Research, National Institutes of Health, Bethesda, Maryland. The funder had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

This study was approved by the Duke University Medical Center Institutional Review Board (#Pro00019233), the University of North Carolina at Chapel Hill Biomedical Institutional Review Board (#09-1882), and the University of Alabama at Birmingham Institutional Review Board (#F110202004). All study participants provided written informed consent.

Author Disclosure Statement

No competing financial interests exist.

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