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Strategies to enhance the therapeutic efficacy of antidepressants: targeting residual symptoms

Benji T Kurian, MD, MPH,
Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9119, USA, Tel.: +1 214 648 0158, Fax: +1 214 648 0167

Tracy L Greer, PhD, and
Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9119, USA, Tel.: +1 214 648 0156, Fax: +1 214 648 0167

Madhukar H Trivedi, MD†
Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9119, USA, Tel.: +1 214 648 0181, Fax: +1 214 648 0167

Abstract

Major depressive disorder (MDD) is an illness of great morbidity that affects many people across the world. The current goal for treatment of MDD is to achieve remission (i.e., no depressive symptoms). However, despite scientific advances in the treatment for MDD, antidepressants as first-line agents yield only modest remission rates. In fact, a recent study indicated that only one out of three subjects who received a standard, first-line antidepressant attained remission. Not achieving remission from depressive symptoms increases the risk of a more chronic and debilitating course of illness with frequent recurrences. Although a number of reasons contribute to these modest outcomes, the presence of residual symptoms is a major problem. Residual symptoms are defined as symptoms that linger despite an adequate dose and duration of an antidepressant medication. This article reviews the prevalence and clinical impact of common residual symptoms and discusses the utility of aggressively addressing residual symptoms to enhance the efficacy of antidepressant medications.

Keywords

antidepressant medication; augmentation strategy; depressive subtype; major depressive disorder; remission; residual symptom

†Author for correspondence Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9119, USA, Tel.: +1 214 648 0181, Fax: +1 214 648 0167, E-mail: madhukar.trivedi@utsouthwestern.edu.

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Major depressive disorder

Major depressive disorder (MDD) is a common illness of significant severity and burden, with a lifetime risk of up to 25% in women and 12% in men [1]. According to the WHO, depressive disorders are the fourth leading cause of disability-adjusted life years worldwide, and by 2020 are estimated to be second only to ischemic heart disease [2]. A recent analysis on the effect of mood disorders on work performance conducted by Kessler and colleagues revealed that MDD is associated with 27.2 lost work-days per ill worker per year [3]. Given the high prevalence and significant morbidity associated with MDD, identifying effective and tolerable therapeutic strategies to achieve patient remission (i.e., freedom from depressive symptoms) are imperative. In recent years, the American College of Neuropsychopharmacology Task Force has established remission as the goal of treatment for patients with MDD [4]. The consequence of not achieving remission is that patients with residual depressive symptoms (i.e., nonremission) have an increased risk for MDD and a shorter time to relapse of symptoms [5].

Currently, antidepressant medications are the most common form of treatment for adults suffering from MDD, with the selective serotonin-reuptake inhibitors (SSRIs) being the most commonly prescribed agents in the USA [6]. However, based on recent effectiveness trials, only one out of three depressed out-patients receiving first-step treatment with an SSRI achieved remission from depressive symptoms [7]. In other words, two-thirds of patients receiving a first-step treatment with an SSRI will not achieve remission and are at risk for relapse. Successive treatment steps lead to diminishing remission rates. Other large multicenter trials in chronically depressed out-patients confirm the modest remission rates found in The Sequenced Treatment Alternatives to Relieve Depression (STAR∗D) trial [8,9]. In addition, while Hennings *et al.* found higher rates of remission (57.9%) among their depressed in-patients, the authors still report a high rate of patients not achieving remission (42.1%), despite an average in-patient hospitalization of nearly 12 weeks [10]. The authors further report that nonremitters were more likely to have a longer episode duration and a higher percentage of treatment resistance, similar to out-patient effectiveness trials in depression. Therefore, novel strategies to enhance the therapeutic efficacy of antidepressant medications early in the course of treatment are warranted.

Residual symptoms associated with MDD

The treatment of MDD is complicated by high rates of residual symptoms (i.e., partial- and non-responders to antidepressant medications) and associated treatment response heterogeneity, which is reflected by modest first-step remission rates. Two types of residual symptoms are commonly described:

- Residual symptoms that are classically depicted as continued manifestations of core depressive symptoms (i.e., impairments in sleep, interest, guilt, energy, cognition, appetite, psychomotor activity, suicidal ideation and depressed mood);
- Residual symptoms that co-occur as nonclassic symptoms of MDD (i.e., anxiety, pain, irritability and cognitive impairments) (Table 1).

While traditional antidepressants are utilized to target core depressive symptoms, this second class of noncore residual depressive symptoms has limited data regarding antidepressant treatment efficacy and symptom resolution. Regardless of the symptom type, residual depressive symptoms increase the risk for relapse and are associated with psychosocial impairments and a more chronic course of illness [11,12].

Traditional treatment strategies for residual symptoms have included switching to another agent or augmenting the original antidepressant with an additional medication. The STAR∗D

study revealed that both of these strategies are efficacious and the decision to switch or augment should be based on treatment response, tolerability (i.e., side effects) and patient preference [13]. A novel strategy with limited evidence, however, is to initiate therapeutic combinations at the onset of treatment to enhance efficacy and hasten time to remission [14]. Employing switch, augmentation and combination strategies to treat MDD are part of a new initiative to personalize the treatment of MDD such that patients achieve a more complete functional recovery. In fact, the Strategic Plan of the National Institute of Mental Health's recognizes the need to target and personalize the treatment of individuals with mental illness [15]. In the plan, Strategy 3.2 aims to 'expand and deepen the focus to personalize intervention research.' As a part of this strategy, it is suggested that traditional outcome measures used in clinical efficacy studies be expanded to include functional measures and 'other indicators of recovery', which must include targeted symptoms and specific symptom profiles. It is hoped that this more personalized treatment will provide depression and other mental illness patients with more thorough recovery.

The decision to switch versus augment an inadequate existing treatment can be difficult. In general, if a patient has difficulty tolerating a medication or if an adequate dose and duration produces little or no response, switching to a new agent is considered. However, one potential drawback of switching medications is that the initial medication may have required additional time to achieve efficacy. Additionally, for individuals whose depression has responded but residual symptoms have persisted, switching may extend the time it takes to achieve remission. In these settings, augmentation strategies are often preferred. Ideally, augmentation strategies should enhance the action of the initial antidepressant medication, thereby reducing residual symptoms and/or achieving remission. A number of agents are currently used clinically for augmenting primary antidepressants, of which lithium and triiodothyronine (T_3) are most commonly used as first-line augmenting agents [16–20]. In fact, Bauer and colleagues found that lithium, when used as an augmentation agent, in the continuation phase of treatment for MDD is effective in preventing relapse [17]. In addition to these conventional agents, recent studies have shown that nontraditional agents, such as modafinil, can be effective in reducing residual symptoms associated with depression [21]. While it is important to target augmentation treatments to reduce symptoms of the overall depressive syndrome, a number of augmentation agents are targeted at alleviating specific residual symptoms (e.g., anxiety, insomnia/fatigue and cognitive impairments) and thereby enhancing the efficacy of first-line antidepressants (Table 2).

Anxious depression

Symptoms of anxiety and comorbid anxiety disorder diagnoses are quite common in individuals with MDD. In fact, comorbid symptomatology and diagnoses are believed to be more prevalent than isolated disorders [22]. The presence of anxiety along with depression can result in treatment resistance, residual symptoms and functional impairment.

Anxious depression has been defined both dimensionally as MDD with elevated or significant anxiety symptoms (e.g., a 17-item Hamilton Depression Rating Scale anxiety/somatization factor score of ≥7) [23], and syndromally [23] based on the presence of a comorbid anxiety disorder (e.g., meeting criteria for both MDD and a comorbid anxiety disorder [24]). Symptoms of anxiety can include both psychic anxiety (e.g., feelings of worry, tension, irritability and fearfulness) and somatic anxiety (e.g., physical complaints, such as aches and pains or gastrointestinal problems). Such symptoms can be assessed by independent measures developed to evaluate anxiety (e.g., the Hamilton Rating Scale for Anxiety), as well as by examining symptom clusters from other symptom severity scales, such as the anxiety/somatization factor score from the 17-item Hamilton Depression Rating Scale, as discussed in the aforementioned example [23].

Prevalence & clinical impact of anxious depression

Almost 60% of patients with MDD have a comorbid anxiety disorder [25], with generalized anxiety disorder being the most common [26]. When anxiety is measured dimensionally, as in the large STAR∗D study, the prevalence of anxious depression is approximately 53.2% [27]. Most anxiety disorders will precede MDD approximately two-thirds of the time [26,28,29].

The combination of depression and anxiety is more disabling than either disorder alone, resulting in an increased risk of suicide, alcohol and substance abuse, impairment in everyday activities, social dysfunction, poorer perception of health, and increased comorbid medical conditions [28,30,31]. Furthermore, somatic symptoms of anxiety in depressed patients can increase the likelihood that a moderate-to-severe side effect will be reported during the course of antidepressant treatment [32].

Treatment of anxious depression

Comorbid depression and anxiety can influence treatment choice and outcome [33], as different presentations of anxiety symptoms and/or diagnoses can differentially affect the patient's functioning, as well as the selection of and response to treatment.

Broad-spectrum agents, such as SSRIs, are often considered to be first-line therapy for comorbid depression and anxiety owing to their established efficacy in the treatment of both disorders and their favorable tolerability profile [28,34]. Serotonin–norepinephrine-reuptake inhibitors (SNRIs) are becoming increasingly popular as a treatment choice for depression and anxiety. In fact, the SNRI venlafaxine has been shown to be superior to placebo and to fluoxetine in the treatment of comorbid depression and anxiety [35], resulting in earlier improvements and higher remission rates in moderately and severely anxious depressed patients, particularly those with psychic anxiety. While less data are available, duloxetine also has some efficacy for MDD and anxiety [36]. Combining SSRIs or SNRIs with benzodiazepines may increase treatment response, yielding benefits both with respect to speed of response and overall response [34]. However, the side-effect profile of these agents makes monitoring their use essential and may also preclude long-term use of these agents.

Patients with anxious depression may need to be monitored more frequently and for a longer duration than patients with isolated disorders. For example, depressed patients with comorbidity have demonstrated delays in improvement for depressive and anxious symptoms compared with noncomorbid patients [25]. Dunner *et al.* recommend that depressed patients with comorbid panic disorder or obsessive–compulsive disorder should be evaluated for a minimum of 9–12 weeks before determining the efficacy of a particular treatment [28].

In addition to lengthened acute-phase treatment, other specific treatment recommendations for anxious depression include comprehensive symptom assessment, a comprehensive treatment approach (e.g., augmentation or combination strategies), the use of a treatment algorithm, education of physicians and patients, and a focus on remission as the goal of treatment, which includes a goal of minimal to no symptoms and restoration of function [29].

Insomnia & depression

Prevalence & clinical impact of insomnia

Many people in the general population complain of insomnia [37]. In patients with MDD, this complaint is heightened, where up to 90% present with comorbid insomnia [38]. Insomnia is a core symptom of MDD and the frequency with which it occurs suggests how integral a role it plays in achieving remission and avoiding residual symptomatology. Furthermore, Nierenberg and colleagues assessed the prevalence of residual symptoms in a sample of 215

patients taking open-label fluoxetine 20 mg for 8 weeks; of the original sample, 108 achieved remission (17-item Hamilton Rating Scale for Depression score of ≤7), yet 44% continued to complain of problems with sleep (either insomnia or hypersomnia) [39]. To this extent, studies have consistently found that depression and concurrent insomnia predispose to future episodes of depression and anxiety [37,40].

One of the difficulties in identifying insomnia as a residual symptom in MDD relates to antidepressant treatment-emergent insomnia [41]. The incidence of antidepressant-induced insomnia varies according to the agent prescribed; however, this phenomenon is most commonly described among second-generation antidepressant agents [41]. Although the association of sleep disturbances in MDD is complex and can present from being a core symptom of MDD to a side effect of antidepressant medication treatment, insomnia is undoubtedly a symptom that, if left untreated, can portend a poor clinical outcome.

Treatment of insomnia & depression

For a number of years, clinicians have been prescribing hypnotic medications, such as benzodiazepines, to treat MDD and concurrent insomnia. However, due to the side-effect profile associated with these older benzodiazepines, newer nonbenzodiazepine hypnotics (i.e., zolpidem, zaleplon and eszopicolone) have emerged. Furthermore, recent studies have shown improvements in sleep for subjects taking an SSRI and zolpidem or eszopicolone concurrently [42,43]. Ramelteon, a novel medication indicated for primary insomnia that works as a melatonin-receptor agonist, may also warrant study in patients with MDD and residual insomnia [44]. Lastly, while sedating antidepressants, such as mirtazapine, trimipramine and amitriptyline, are often prescribed in routine clinical practice for patients with MDD and concurrent insomnia, little evidence supporting their long-term use is available [38,44,45].

Fatigue/daytime sleepiness & depression

Prevalence & clinical impact of fatigue

Another common residual symptom associated with MDD, and often concurrently occurring with insomnia, is daytime sleepiness and fatigue [41]. Fatigue is a hallmark of chronic fatigue syndrome and fibromyalgia, both of which are commonly comorbid with MDD [46]. In the same clinical sample of patients taking fluoxetine, Nierenberg *et al.* found that, despite achieving remission, 38% of patients continued to complain of fatigue [39].

Similar to the diagnostic complexity surrounding insomnia in depression, fatigue also poses an interesting dilemma. Fatigue or decreased energy can also present as a core symptom of MDD, a residual symptom in the course of treatment or a treatment-emergent side effect. Often, insomnia and fatigue present conjointly, as difficulties with sleep may predispose to symptoms of fatigue [41]. In such situations it is important to accurately diagnose the constellation of symptoms and avoid any potentially offending agents (i.e., treatment-emergent insomnia/daytime fatigue) [41]. In addition, recent evidence points to a potential relationship between obstructive sleep-disordered breathing and MDD [47,48]. While it is probably premature to screen for obstructive sleep disorders in patients with MDD, given the overlapping symptom clusters, it is worth further investigation.

Treatment of daytime sleepiness & depression

Baldwin and Papakostas recommend three treatment strategies for patients suffering from MDD and daytime sleepiness [49]:

- Avoid antidepressant agents likely to exacerbate daytime sleepiness (i.e., mirtazapine)
- Consider antidepressant agents likely to improve daytime sleepiness (i.e., bupropion)

- Consider antidepressant augmentation strategies

Recent studies have assessed the use of treatments to augment conventional antidepressant medications in patients with residual daytime sleepiness/fatigue. Papakostas and colleagues found preliminary evidence for the use of atomoxetine, a selective noradrenergic-reuptake inhibitor [50], when added to traditional antidepressants (mostly SSRIs) for the treatment of residual fatigue [51]. However, this was an open-label study that was additionally limited by a small sample size. Furthermore, Michelson and colleagues compared the efficacy of atomoxetine with placebo in sertraline nonresponders and, while no significant improvement in overall depressive efficacy was found, atomoxetine augmenters tolerated treatment well, with dry mouth, insomnia and constipation being the only adverse effects occurring in significantly greater proportions than placebo augmenters [52]. With regards to randomized, placebo-controlled studies, Fava and colleagues found modafinil augmentation to have a modest effect in treating residual fatigue in MDD, while the only side effects to occur more frequently than with placebo were nausea and jitteriness [21,53]. Minzenberg and colleagues postulate that modafinil largely affects brain catecholamines, inhibiting both the dopamine transporter and the norepinephrine transporter, and elevating the extracellular concentrations of glutamate, serotonin and histamine, while also activating the orexin system and decreasing GABA in the neocortex [54]. Larger, more definitive trials to assess the efficacy of atomoxetine and modafinil are necessary to solidify their place in the clinician's pharmacologic armory.

Cognitive impairment & depression

Disrupted cognitive function is a common complaint of depressed individuals and can significantly impair daily functioning. Cognitive function can be difficult to define owing to the breadth of domains that may be assessed. With respect to the core symptoms of depression, attention and decision-making are specifically assessed. Neuropsychological tests, which are the most frequently used measurements of cognitive function, assess a vast array of cognitive abilities. In a meta-analysis of neuropsychological function in depression, Veiel reports that performance on tasks involving acquisition, retention and retrieval on both verbal and nonverbal learning measures revealed moderate levels of impairment among depressed subjects [55]. However, reports of performance on these measures demonstrated the highest amount of between-study variability, suggesting that learning measures in general have not been reliably assessed in depression. Veiel concluded from his meta-analysis that depressed individuals exhibit global diffuse cognitive impairment, with particular impairment in the frontal lobes.

The most reproducible deficits have been shown in the domains of attention, executive function and verbal learning and memory. Coull defines attention as "the appropriate allocation of processing resources to relevant stimuli" [56]. A variety of aspects of attention have been defined, ranging from orienting attention to divided attention. Executive functioning is typically defined as the capacity for mental flexibility, set-shifting ability and the overall ability to mentally plan and organize and/or manipulate information [57,58]. Verbal learning is most often assessed with respect to acquisition, recall and recognition. Additionally, recent studies have implicated deficits in working memory (i.e., faulty mental processing) in patients with MDD [59,60].

Prevalence & clinical impact

The prevalence of cognitive impairment in depression has not been well evaluated; however it is clearly a common occurrence given that it is one of the nine core symptoms of MDD. In fact, Fava and colleagues reported that among patients responding to antidepressant treatments, over 30% continue to report residual cognitive impairments (i.e., apathy, inattentiveness, forgetfulness, word-finding difficulty and/or mental slowing) [61]. Many of the tasks that have

been most frequently noted as impaired in depressed individuals are directly relevant to carrying out activities of daily living, managing home life and maintaining one's livelihood. For example, attentional impairments that have been noted on measures of mental control and orientation [62], selective attention [63], directed attention [64] and sustained attention [65] could adversely impact one's ability to focus on a job or at school and to carry out tasks to completion. Similarly, some of the most pronounced impairments observed in depression are on executive function or working memory tasks requiring mental flexibility and control [66–71]. Such impairments can result in adverse functional consequences. Certainly, the ability to acquire, retain and recall verbal information is essential in daily life and difficulties with these functions create problems with daily activities. Interestingly, Naismith *et al.* found moderate relationships between psychomotor speed and physical disability, as well as memory retention and mental-health disability, supporting the relationship between cognitive impairment and disrupted function [72].

Cognitive impairments may contribute to impaired functioning independently of depressive symptoms, further illustrating the need to have specific, targeted treatments for such impairments. Jaeger *et al.* found that measures of attention, ideational fluency, visuospatial function and learning were strongly associated with impaired life functioning, even after controlling for residual depression, psychosis and disabling medical comorbidities [73]. Similarly, Paelecke-Haberman *et al.* found that deficits on some measures of attention and executive function remained in euthymic, remitted depressives [74], further illustrating the need to target these symptoms during treatment and adequately monitor their outcomes.

Treatment—Few studies have targeted cognitive symptoms in depression. Some potentially beneficial augmentation agents that may result in cognitive benefits include psychostimulants [49,75,76], modafinil [77] and cholinesterase inhibitors [78,79]. It should be noted that the positive augmentation studies with psychostimulants have been performed in elderly populations and were not specifically targeting cognitive deficits, and the use of modafinil to improve cognitive function has yielded modest improvements at best. In addition, the tolerability of these agents makes them undesirable treatment choices. Alternative strategies, such as the use of cognitive remediation or nutritional supplements such as citicoline, need to be investigated in order to find effective, tolerable treatments for cognitive impairments. It is imperative that we find treatments that will target this disruptive problem.

Other residual symptoms

Irritable depression

Although not officially recognized as a subtype of MDD, irritability is a common symptom presentation in clinical practice. In fact, results from STAR∗D revealed that 40% of the initial sample (1456 patients) reported irritability more than half of the time [80]. This is congruent with prior studies that report irritable symptoms ranging between 34 and 60% in depressed patients [81–83]. Perlis and colleagues further defined the subset of patients with irritable symptoms, finding that irritability also correlated with poor quality of life, impaired functional status and worse overall depression symptom severity [80].

Treatment—A common dilemma facing clinicians when a patient presents with depression and irritability is differentiating unipolar MDD from bipolar disorder. Akiskal and colleagues addressed this question by conducting a study of 254 unipolar depressed patients to assess the prevalence of agitated depression and whether it was associated with symptoms commonly linked to bipolar disorder [84]. Currently, evidence supporting treatment for irritability in unipolar MDD is lacking; however, future trials need to focus on this common symptom.

Pain (somatic symptoms) & depression

Physical (somatic) complaints are a common symptom presentation in patients with MDD. In fact, Simon and colleagues found that up to 69% of patients with depression reported having only somatic symptoms [85]. Additionally, physical symptoms often persist even after traditional emotional symptoms improve. Ohayon *et al.* reported that patients with concurrent chronic pain disorders and MDD suffer from longer depressive episodes than patients without chronic pain disorders [86].

Somatic depression is more commonly found in women and appears to co-occur with anxiety disorders [87]. Based on results from STAR∗D, Husain and colleagues reported that depressed patients presenting with pain were also more likely to be younger, African–American, Hispanic and less educated than depressed patients without co-occurring somatic symptoms [88]. This study also found that patients with somatic presentations were more likely to report anxious features. Lastly, a number of syndromes (i.e., fibromyalgia [89]) exist in which somatic and depressive symptoms commonly co-occur.

Treatment—Targeting treatment strategies for physical symptoms in MDD has primarily focused on shared neurobiological pathways for pain and depression. Specifically, serotonin and norepinephrine, which are key neurotransmitters in descending inhibitory pain pathways and are associated with the modulation of ascending pain signals, have increased availability in pain and depression. Clinically, SNRIs, such as duloxetine, have proven efficacy and have a US FDA-approved indication for treating pain conditions (i.e., fibromyalgia and diabetic neuropathy) [90]. Older tricyclic antidepressants, such as amitriptyline (which has an FDA-approved indication for polyneuropathy), have a long treatment history for a variety of chronic pain conditions [91]. However, the tolerability and side-effect profile may limit the utility of tricyclic antidepressants for certain patients. Lastly, some anticonvulsants (e.g., gabapentin and pregabalin) do have approved indications for chronic pain disorders and, therefore, studies assessing the role of these agents for patients with MDD and concurrent pain are warranted [92]. However, given the lack of evidence of these agents in patients with chronic pain and depression their current use is not advocated.

Expert commentary

Despite new antidepressant medications with improved tolerability, the majority of patients prescribed a first-step treatment will not achieve remission. Furthermore, based on results from STAR∗D, those who fail to remit after first-step treatment have a modest chance of remitting after their second treatment (31%) [93]. Subsequent treatment stages, however, prove to have diminishing returns, which raises the question – how early should augmentation and combination treatments be initiated in the course of MDD? Based on our clinical experience, this should be determined systematically while paying close attention to objective measures of symptom severity, functional outcome and side-effect burden. These three domains constitute a larger construct known as measurement-based care (MBC) [7,94]. The primary goal of MBC is to individualize antidepressant treatment and dosing in an effort to minimize the side-effect burden and maintain safety, while enhancing the therapeutic efficacy for each patient [7,94]. Utilizing a treatment strategy such as MBC in clinical practice provides objective evidence to address key antidepressant treatment questions, such as: at which dose, for which duration and when to switch or augment? In addition, routinely measuring symptoms of depression provides information on the emergence of residual symptoms that may warrant treatment. Once a residual symptom is identified and a treatment initiated, MBC can also provide ongoing monitoring for symptomatic improvement and side-effect burden.

Evidence-based psychotherapies (EBPTs) represent another avenue by which to enhance the efficacy of antidepressant medications and achieve a full, sustained remission of depressive

symptoms. EBPT has earned a name both as a monotherapy or as part of combination treatment with antidepressants in achieving remission in depressed patients [95]. While we wait for novel treatments to improve remission rates in MDD, it is imperative that we enhance our current treatment approaches (antidepressant medications and EBPT) by identifying residual symptoms and treating them aggressively, yet systematically [95].

Five-year view

In recent years, emphasis has been placed on personalizing antidepressant medications based on predictors of treatment response [96]. However, baseline predictors of antidepressant treatment response have not yielded clinically significant findings. The heterogeneity of the depressed phenotype most likely plays an important role in modest first-step remission rates and variable predictors of treatment response. Additionally, the availability of antidepressant treatments across the world, especially in Europe, compared with in the USA is quite variable. For example, agomelatine, which works as a melatonin agonist and SSRI, is approved in Europe and shows promise as an agent for depressed patients with concurrent insomnia [97]. In the next 5 years, further steps will be made to integrate basic scientific discoveries (i.e., neuroimaging and genetics) that better delineate depressive subtypes and impact treatment decisions [98–102]. Until that time, enhancing the efficacy of antidepressant treatments resides in objectively measuring depressive symptoms and aggressively treating residual symptoms to remission while maintaining a favorable side-effect profile.

Key issues

- First-line treatments for major depressive disorder (MDD) result in remission for only approximately a third of treated patients.
- Failure to achieve remission (i.e., the presence of residual symptoms) results in poorer prognosis for depressed individuals by increasing the likelihood of relapse, contributing to continuing, or even worsening, functional impairments and causing a more chronic course of illness.
- Strategies that can enhance the therapeutic efficacy of antidepressants include augmentation, switching or combination treatments.
- The personalization of treatment may be accomplished by targeting specific symptoms or symptom clusters in order to help patients achieve full, functional recovery. Currently, the National Institute of Mental Health strategic plan identifies such a goal as part of their initiative.
- Anxious depression can be defined by the presence of MDD along with elevated symptoms of anxiety or a comorbid anxiety disorder diagnosis. Currently, treatments for anxious depression most often include selective serotonin-reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors (SNRIs), with benzodiazepines added to increase the speed of response and overall response.
- Insomnia can present as initial or middle insomnia, or early-morning awakening. Insomnia has historically been treated predominantly with benzodiazepines, but recent nonbenzodiazepine hypnotics (i.e., zolpidem, zaleplon and eszopicolone) have been developed that have a more favorable side-effect profile.
- Strategies to treat fatigue and/or daytime sleepiness include: avoidance of antidepressant agents (e.g., mirtazapine) that are likely to exacerbate daytime sleepiness; consideration of antidepressant agents (e.g., bupropion) that are likely to improve daytime sleepiness; and consideration of antidepressant augmentation

strategies. Limited data suggest that atomoxetine and modafinil may hold benefit for fatigue/daytime sleepiness, although more definitive studies are needed.

- Cognitive impairments in depression are most often noted in measures of attention, executive function and verbal learning. While agents such as psychostimulants, modafinil and cholinesterase inhibitors may have benefits for cognitive function, their effects are not robust and they do not have favorable side-effect profiles, thus illustrating the need to develop better treatments for these symptoms.
- Measurement-based care can enable us to individualize antidepressant treatment and dosing in an effort to minimize side-effect burden and maintain safety, while enhancing the therapeutic efficacy for each patient.

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Table 1

Commonly occurring residual symptoms in major depressive disorder.

Symptom/subtype	Prevalence (%)	Clinical impact
Anxiety	46–60*	When present with MDD, increases rates of suicide and comorbidities
Insomnia	44	Must discern whether insomnia is true residual symptom or a side effect of ATDs
Fatigue/daytime sleepiness	38	Rule out other causes: ATD side effect, obstructive sleep apnea
Cognitive impairment	30	Most replicated deficits occurring with attention, executive function, verbal learning and memory
Irritability	34–66*	Irritability correlates with poor quality of life, impaired functional status and worse depression severity
Pain (somatic symptoms)	69*	More likely to be younger, African–American or Hispanic and less educated

* Prevalence reflects percentage co-occurring with MDD, not explicitly as a residual symptom.

ATD: Antidepressant; MDD: Major depressive disorder.

Table 2

Adjunctive treatment for residual symptoms associated with major depressive disorder.

Residual symptom	Medication	Dose range (mg/day)	Dosing schedule
Anxiety	BZD: lorazepam	0.5–2	Every 4–6 h prn
	Non-BZD: buspirone	20–60	Two- or three-times daily
Insomnia	Consider switching to a more sedating antidepressant		
	Zolpidem	5–10	Once daily at bedtime
	Zolpidem CR	6.25–12.5	Once daily at bedtime
	Zaleplon	5–10	Once daily at bedtime
	Eszopiclone	1–2	Once daily at bedtime
	Ramelteon	8	Once daily at bedtime
Fatigue, daytime somnolence	Modafinil	200	Once daily in the morning or once daily
	Atomoxetine	40–80	Once daily
Cognitive impairment	Methylphenidate	5–20	Twice daily
	Donepezil*	5–10	Once daily at bedtime
	Galantamine*	8–16	Twice daily
	Modafinil	200	Once daily in the morning or once daily
	Citicoline	500–2000	Once daily
Irritability	No evidence to date supporting adjunctive treatment		
Pain (somatic) symptoms	Duloxetine‡	30–60	Once daily
	Venlafaxine XR	75–225	Once daily
	Amitriptyline§	25–150	Once daily at bedtime

*Methylphenidate, donepezil and galantamine trials were conducted in older adults with depression.

‡Duloxetine has US FDA-approved indication for use in fibromyalgia and diabetic neuropathy.

§Amitriptyline has FDA-approved indication for use in polyneuropathy.

BZD: Benzodiazepine; prn: *Pro re nata*.