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PSYCHIATRY IN PRIMARY CARE (BN GAYNES, SECTION EDITOR)

Treatment Resistant Depression: Strategies for Primary Care

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Abstract Depression is commonly diagnosed and treated in primary care. Recent evidence indicates that the majority of depressed patients will not fully recover with an initial antidepressant treatment. This paper reviews commonly used options for treatment after an inadequate initial antidepressant response. The alternatives range widely, and include escalating the dose of the initial antidepressant, switching to an alternative medication, combining two antidepressants with different mechanisms of action (e.g., bupropion + SSRI or mirtazapine + venlafaxine), adding other medications such as lithium or certain atypical antipsychotics (olanzapine, aripiprazole, or quetiapine) to the antidepressant, adding a natural product such as l-methylfolate or s-adenosylmethionine (SAMe), or adding cognitive behavioral psychotherapy. What agent to be used will depend on the comfort level of the primary care practitioner and the availability of Psychiatry referral. However, it is reasonable to take one or more additional steps to attempt to achieve remission.

Keywords Depression · Antidepressants · Treatment-resistant depression · Augmentation · Combination therapy · Antidepressant switch · Complementary and alternative therapy · Psychotherapy · Psychiatry · Primary care

Introduction

Primary care physicians (PCP) must be knowledgeable about treatment options for depression since many patients with major depression first seek care from their PCP. The selective serotonin reuptake inhibitors (SSRIs) medications have become the first-line choice for most patients presenting to primary care with major depression given their good tolerability and safety profiles. The serotonin-norepinephrine reuptake inhibitors (SNRI) venlafaxine, desvenlafaxine, and duloxetine, the atypical antidepressants bupropion, which acts predominantly on norepinephrine and dopamine, and mirtazapine, a dual serotonin and norepinephrine agent, are also common first-line choices. Unfortunately, the majority of patients treated with an initial trial of an SSRI do not achieve remission. In the NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial, only 27.5 % of patients achieved remission after up to 14 weeks of treatment with citalopram [1]. By comparison, a 2010 review of 91 antidepressant monotherapy randomized controlled trials, which typically exclude many patients with medical and psychiatric comorbidities, still only found an average remission rate of 44 % [2•]. This means that in clinical practice a minority of patients treated with an antidepressant will achieve sufficient response and most will require an advanced treatment option. There are three commonly used medication options after an initial failed trial: switching to an antidepressant of a different class, combining two antidepressants with different mechanisms of action, and augmentation, which is combining the initial antidepressant with a non-antidepressant option.

Many patients do not experience full remission with an initial antidepressant medication, but there may be issues that should be considered prior to one of the alternatives described below. For example, there may be co-occurring medical problems such as hypothyroidism, fibromyalgia, myalgic encephalomyelitis, sleep disturbances, early Parkinson's disease or dementia, or some medications, including oral corticosteroids, opiates, benzodiazepines or other sedatives, metaclopromide, or other drugs, that may be causing or aggravating the depressive symptoms. In addition, non-adherence to treatment is common, occurring in as many as half of patients prescribed antidepressants [3]. Simple interventions including more intensive patient education about medications may reduce non-adherence. In addition, ongoing stressors such as family

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or marital problems may adversely affect mood, in which case therapy is indicated.

Switching

After failing to achieve remission following an initial trial with an SSRI, one strategy is to discontinue the medication and start a new monotherapy. The key question here is whether to try a different SSRI, a different class of antidepressant such as a selective serotonin norepinephrine reuptake inhibitor (venlafaxine, duloxetine, or desvenlafaxine), or an atypical antidepressant such as bupropion or mirtazapine. A 2011 review by Connolly and Thase [4••] found that two of four randomized trials found switching from an SSRI to the SNRI venlafaxine to be superior to a trial of a second SSRI, although they note that one of these two was not clinically meaningful, with a number needed to treat (NNT) of 13. The STAR*D trial examined venlafaxine XR as one of the agents for switching treatment strategies and achieved remission in 24.8 % of patients with this agent, but this was not significantly different from any of the other switching or augmentation strategies in this trial [5–7]. There is a paucity of data for the other SNRIs.

Bupropion is another medication that clinicians may try after failure of an SSRI. In STAR*D, the remission rate after switching to bupropion was comparable to that of venlafaxine XR or sertraline [1, 5]. There are no other randomized controlled trials of bupropion for treatment-resistant depression [4••]. However, bupropion has fewer sexual side effects than SSRI's and SNRI's and it is an option when sexual dysfunction is a problem [8].

Mirtazapine has had mixed results when studied for treatment resistant depression. One RCT compared switching to sertraline with switching to mirtazapine after failure of an SSRI. Mirtazapine had a remission rate of 38 % compared to 28 % for sertraline, although this was not statistically significant. Another trial compared mirtazapine with venlafaxine as a monotherapy after failure of an SSRI and found venlafaxine superior [4••].

A switch from an SSRI or SNRI to either a tricyclic antidepressant (TCAs) or a monoamine oxidase inhibitors (MAOIs) is supported by a limited amount of data [4••]. The higher risk of side effects with either, the potential lethality of TCAs in overdose, and the dietary restrictions and potential for serious adverse effects (e.g., hypertensive reactions) of MAOIs will typically limit their use as antidepressants in primary care. Individual clinicians may be comfortable prescribing these medications, but they are not generally recommended in primary care practice.

Support for switching antidepressant medications is limited and the results have been mixed with no strategy being clearly superior. Therefore, antidepressant switches are often done empirically to take advantage of effects with specific medications. As noted earlier, bupropion may be a good choice for a patient who is experiencing sexual dysfunction due to SSRI or SNRI therapy. A patient with poor sleep and appetite may benefit from a trial of mirtazapine, considering its side effect profile of sedation and appetite stimulation, although some patients may experience excessive weight gain [9]. It also has a low potential for gastrointestinal side effects owing in part to the fact that it blocks serotonin 3 receptors like ondansetron. Finally, cost of care is a consideration with many patients. Even though most of the medications described above are generic, some remain more expensive. This is likely to be pertinent for patients who do not have prescription drug coverage.

High Dose SSRIs

Rather than switching medications after a failed trial of an SSRI, a higher dose may be considered. A 2002 trial by Fava et al. compared high dose fluoxetine (40–60 mg) with augmentation strategies using lithium or desipramine for patients who were nonresponders or partial responders to 20 mg of fluoxetine daily [10]. The high-dose fluoxetine group had a higher response rate, although the difference was not statistically different. Even without a statistical difference in these strategies, many patients and clinicians may find the high-dose SSRI strategy a preferable option, as it does not require laboratory monitoring as lithium therapy does, and typically has a better side effect profile than either TCAs or lithium. Consider a dose increase if there have been minimal side effects and partial improvement on the initial dose [11].

Waiting Longer

While many antidepressant trials assess remission and response rates at 4–8 weeks, it may be worth waiting longer before giving up on the initial strategy and trying a different medication. STAR*D found that many patients who did not achieve remission or response after several weeks of treatment, eventually did achieve remission or response by 14 weeks [12]. Additionally, Fava et al. [10] cited earlier suggested that many patients who responded after raising the dose of fluoxetine may have simply been "slow responders" who needed more than the 8 weeks allowed in their study to respond adequately. An additional three weeks at a standard dose of an antidepressant is a reasonable strategy after a partial effect of an initial trial [13].

Combination Antidepressants

SSRI's plus Tricyclic and Related Antidepressants

Most studies supporting the combination of tricylic and related antidepressants with SSRI's have been of relatively

small scale [14, 15]. However, there are at least two controlled clinical trials supporting the benefit of this type of combination as compared with continuation SSRI therapy with placebo [14, 15]. However, there are potential drug-drug interactions between many SSRI's and tricyclics and plasma level monitoring of the tricyclic antidepressant is recommended with this strategy.

SSRI/SNRI Plus Bupropion or Mirtazapine

Despite relatively weak evidence for their use as augmenting agents, bupropion and mirtazapine are commonly used in combination with SSRI's or SNRI's. Valenstein et al. [16] surveyed antidepressant combinations most commonly used in mental health clinical settings and found that 38 % of combinations included bupropion and 19 % of combinations included mirtazapine.

A 2002 double-blind placebo-controlled study by Carpenter et al. [17] found significant benefit using mirtazapine for antidepressant augmentation after failing antidepressant monotherapy with 45 % achieved remission with mirtazapine added to the initial antidepressant compared with 13 % for placebo. However, this was a small trial with only 26 patients and did not compare augmentation with outright switching to mirtazapine.

An open-label study of bupropion SR by DeBattista et al. [18] found a response rate of 54 % (15 out of 28) when bupropion was added following an inadequate response to an SSRI. Bupropion SR (sustained release) was tested in the STAR*D trial for patients who had failed to achieve remission with citalopram monotherapy and the remission rate was 29.7 %, which was not significantly different from other augmentation or switching strategies used after failure of citalopram [5]. Notably, SSRI+bupropion was more beneficial than SSRI+buspirone in participants with low energy, indicating that SSRI-treated patients with residual fatigue or low energy may respond preferentially to this combination [9]. Surprisingly, there have been no placebo-controlled trials of bupropion as a combination strategy with SSRI's or SNRI's in spite of the fact that it is the most commonly used combination therapy for treatment resistant depression [16].

Augmentation

Lithium

As previously stated, some primary care clinicians may feel more comfortable than others prescribing lithium. Side effects with lithium are common and it requires plasma level monitoring because of its relatively narrow therapeutic index. Approximately 50 % of treatment resistant patients respond to lithium augmentation within 4 weeks, with a minimum daily dose of 800 mg typically being required [19]. While lithium has been more rigorously studied as augmentation with TCAs, a randomized, placebo-controlled double-blind study by Baumann [20] supported the effect of lithium augmentation of citalopram with a 58 % response rate with lithium augmentation compared to 14 % in the placebo arm.

The question of lithium augmentation compared with other strategies is another matter. STAR*D examined lithium augmentation compared with switching to mirtazapine, switching to the TCA nortriptyline or augmentation with T_3. Since this was tested in the third tier of the trial, these patients had already failed monotherapy with citalopram and either a monotherapy or augmentation strategy. There was no significant difference in remission rates between lithium at this stage and its comparators [1].

L-Methylfolate

A recent study by Papakostas et al. [21••] examined the use of L-methylfolate, the biologically active form of dietary folate, as an augmentation strategy for depressed patients who were partial or non-responders to SSRIs. They found a response rate of 32.3 % with 15 mg/day of L-methylfolate compared to 14.6 % for placebo over the course of 2 trials. This yields a NNT of approximately 6, comparable to results with lithium or atypical antipsychotics. It is noteworthy, however, that the remission rates were not statistically significant. The authors of this study note that the patients were only treated for up to 30 days and that higher doses were not tested, so we must await additional studies to see if significant numbers of patients can achieve remission with this augmentation strategy. There is no required laboratory monitoring with L-methylfolate and side effects reported were comparable to the placebo group. Considering its safety and tolerability, L-methylfolate may be a viable augmentation strategy in the primary care setting.

S-adenosyl-L-methionine (SAMe)

SAMe is the major donor for methyl groups in human metabolism [22••]. Data are still limited for treatment of depression with this supplement, especially in the context of treatment-resistant depression. The dose range is typically 100–200 mg/day IM or 800-1200 mg/day orally. Double-blind studies comparing SAM-e to various TCA mono therapies found no significant difference between them. In an open study of patients with treatment resistant major depression, by Alpert et al. [23] found that half achieved remission when SAMe was used as an augmentation strategy. In a recent moderate-scaled controlled clinical trial, Papakostas et al. [24•] compared the addition of 800 mg/day of SAMe (400 mg twice daily) against placebo added to an SSRI in treatment non-responders. Response and remission rates were

higher for adjunctive SAMe (36.1 % and 25.8 %, respectively) than placebo (17.6 % versus 11.7 %, respectively). The NNT for response and remission were about 6 and 7. SAMe augmentation was also well-tolerated and comparable to placebo.

Buspirone

Buspirone is a serotonin 1A receptor partial agonist that is FDA-approved for the treatment of anxiety disorders, but is also commonly used as an augmenting agent in depression. Buspirone was compared to bupropion SR in the STAR*D trial for augmentation with patients who had failed citalopram monotherapy and led to remission in 30.1 %, almost identical to the outcome with bupropion SR (29.7 %) [1]. While there have been positive data from open label studies, two randomized placebo-controlled trials have failed to find a significant benefit from buspirone as an augmentating agent [4••].

Atypical Antipsychotics

There is a large literature supporting the benefit of the combination of atypical antipsychotics such as quetiapine, aripiprazole, or olanzapine with SSRI's after an initial antidepressant failure. However, they pose a significant risk for adverse effects including extrapyramidal symptoms, tardive dyskinesia, and metabolic syndrome. The latter necessitates routine laboratory monitoring of lipids and glucose. The risk of tardive dyskinesia may also be higher than initially thought when these medications were introduced [25]. For these reasons, atypical antipsychotics are seldom used in the primary care setting as antidepressant augmenters.

A meta-analysis by Nelson and Papakostas [26] of remission rates using different atypical antipsychotics for augmentation demonstrated clinical utility for olanzapine, quetiapine, aripiprazole, and risperidone, which have all been examined in randomized controlled trials. It should be noted that while the first three have obtained FDA approval for use as augmenting agents in depression, risperidone has not. While two short-term studies (4 weeks) found short-term benefit using risperidone, a 24 week study did not demonstrate any benefit [4••]. There is only a single open label trial of ziprasidone [27] and no published trials with newer atypicals. Unfortunately, we do not have a direct comparison between any of the atypical antipsychotics and other augmenting or switching strategies, as atypicals were not part of the STAR*D trial. Such a study would be very helpful in clinical decision-making and is sorely needed.

Other Options

Many other approaches have been tried in treatment resistant patients, but few have sufficient support at present [13]. Advanced treatment options such as electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial stimulation all have support in treatment resistant patients [28•], but these are not typical strategies in primary care. In addition, the addition of psychotherapy may be beneficial [29]. However, there is only support for an evidence-based psychotherapy such as cognitive behavioral therapy. The benefit of other therapies remains untested.

Conclusion

Primary care clinicians are the first line in treating depression, and will often be faced with patients who do not experience sufficient response to an initial treatment with an SSRI. There are numerous options for switching and augmentation, as well as the options to increase the dose or wait longer, that have evidence to support their use. However, the STAR*D trial compared numerous switching and augmentation strategies and found no strategy to be significantly superior to another, making the decision of which strategy to choose a difficult one. Keeping this in mind, a PCP must factor in safety, side effect profile, cost, and comfort level with prescribing a particular agent. The primary care clinician also should ensure that each trial of treatment is provided for an adequate dose and duration to maximize the chances of responding. Underdosing in clinical practice is common and a high proportion of patients will discontinue the medication on their own before having a chance to respond [30, 31].

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