switch or augmentation, showing the decreased likelihood of response with subsequent antidepressant trials.

In general, monotherapy with first-line antidepressants (e.g., SSRIs, SNRIs, bupropion, mirtazapine) is preferable to combination treatment with two antidepressants because of the increased potential for drug-drug interactions, adverse effects, and lack of clinical benefit. An SR by Bschor et al. (2018) and an RCT by Tadic et al. (2016) found no difference in antidepressant efficacy, symptom response, remission, adverse effects, and functional status between switching and continuation of antidepressant treatment.(124, 125) An SR by Davies et al. (2019) found no difference in depressive symptoms, remission, adverse events, QoL, and functional status in patients who received mirtazapine augmentation versus placebo augmentation.(126) An RCT by Xiao et al. (2021) evaluated the combination of mirtazapine and paroxetine versus either agent alone.(127) They found no difference in symptom improvement and remission at the end of the eight-week trial. Adverse effects were more common with the combination of mirtazapine and paroxetine and mirtazapine monotherapy than with paroxetine monotherapy (mirtazapine plus paroxetine 43%, mirtazapine 43%, paroxetine 22%, p=0.0153). Therefore, in patients with partial or no response to initial treatment, it is reasonable to consider switching to another first-line antidepressant (either within-class or out-of-class), psychotherapy, or augmenting current therapy with psychotherapy or an SGA.

Combined pharmacotherapy and psychotherapy are options if a response or remission is not achieved with an antidepressant as initial monotherapy. In an SR by Li et al. (2018) where the comparators were TAU (three RCTs), psychoeducation (one RCT), health enhancement program (one RCT), and medication change (one RCT), which included participants who were receiving pharmacotherapy at baseline, the addition of psychotherapy (i.e., CBT) resulted in improvement in symptoms of depression and remission.(117) Nakao et al. (2018) showed no difference in adverse events between blended CBT and antidepressant medication versus antidepressant monotherapy.(118)

Augmentation with an SGA may also be considered in patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy. Three atypical antipsychotics are FDA-approved for MDD as adjunctive treatment/augmentation: aripiprazole, brexpiprazole, and quetiapine-XR. Olanzapine is approved for the treatment of acute treatment-resistant MDD when used in combination with fluoxetine, but olanzapine by itself is not indicated for the treatment of treatment-resistant depression (TRD). Other SGAs such as cariprazine and risperidone, while not indicated, are used off-label for augmentation.

Three SRs have demonstrated the significant benefit of SGAs (alone or augmentation) for remission in MDD. Komossa et al. (2010) (28 RCTs) demonstrated significant improvement in remission with aripiprazole (mean doses = 11 – 12 mg/day), olanzapine (mean doses = 8 – 14 mg/day), quetiapine (mean doses = 180 mg/day), and risperidone (mean doses = 1.2 – 1.6 mg/day).(128) Santaguida et al. (2012) (one RCT) demonstrated small significant benefit favoring augmentation with atypical antipsychotics (olanzapine, aripiprazole, risperidone, and quetiapine).(129) Dold et al. (2020) (23 RCTs) demonstrated significant improvement in depressive symptoms with SGAs (aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine).(130) Risperidone augmentation did not differentiate from placebo augmentation.